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OXYGEN UTILIZATION OF THE ORGANISM AND ITS REGULATION

by N. A. Agadzhanyan, et al.

Abstracts of Papers Presented
at a Symposium Held in Kiev-Kanev on May 24-29, 1965.
Kiyevskaya Knizhnaya Tipografiya, Kiev, 1965.

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OXYGEN UTILIZATION OF THE ORGANISM AND ITS REGULATION

Abstracts of Papers for the Symposium

Kiev - Kanev

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OXYGEN UTILIZATION OF THE ORGANISM AND ITS REGULATION

A collection of excerpts from papers on the oxygen metabolism in mammals, under conditions of hypoxia, includes topics on: effect of induced hypoxia in trained and untrained human subjects; oxygen utilization control by regulatory mechanisms; psychological and biochemical aspects of altitude hypoxia; biological oxidation. Some conclusions based on results of animal and human experiments, readings of cardiograms, electroencephalograms, pneumotachometry, etc. comprise: Systematic training, up to hypoxia, during postnatal ontogenesis decreased the oxygen (energy) consumption and respiratory rate. Animals kept at partial vacuum (180 mm Hg) with body temperature artificially maintained at normal level showed a high mortality rate, proving the protective effect of the natural hypothermia induced by hypoxia. Encephalograms indicated that the cerebral cortex is most affected by hypoxia. The upper limit of partial oxygen pressure for prolonged inhalation is placed at 3 atm. abs. Suggested measures for improvement in body function include increase in ionized oxygen content of inspired air in enclosed space; active physical training under high-mountain conditions; "rational breathing" exercises in the altitude chamber; addition of CO_2 to the respiratory air during hyperventilation to increase the oxygen uptake of the brain; etc.

CONTRIBUTION TO THE QUESTION OF THE LIMIT OF ALLOWABLE OXYGEN CONCENTRATIONS IN SEALED CHAMBERS FOR HUMAN OCCUPANCY AND THE MEANS OF INCREASING RESISTANCE TO HYPOXIA

*/3

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Moscow

This paper is to present the physiological foundation for the principles of the creation of an atmosphere in closed chambers and will give data on the critical oxygen concentration.

The paper presents the results of experimental studies in a rarefied atmosphere from long-term experiments (up to 100 days), in an atmosphere of pure oxygen at simulated altitudes up to 10,000 m (198 mm Hg), and data on the tolerance of animals to explosive decompression after protracted stay in an atmosphere of pure oxygen.

The experimental studies, intended to find effective means of increasing

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* Numbers in the margin indicate pagination in the original foreign text.

the resistance of the organism to hypoxia, permitted a relative appraisal of various methods: altitude-chamber training, administration of drugs and biological stimulants, and acclimatization in high mountains.

SIGNIFICANCE OF THE TWO PATHWAYS OF INTRACELLULAR OXIDATION IN THE ADAPTATION OF THE ORGANISM TO MUSCULAR WORK IN THE STATE OF HYPOXIA

/4

T.A.Allik
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The problem of maximizing operational efficiency of personnel under deficiency of oxygen in the inspired air has recently assumed critical importance. Studies by various authors have shown marked individual differences between subjects similarly trained at low elevations, during adaptation to work under high-mountain conditions. It is therefore necessary not only to develop rational systems of training for these conditions, but also to define criteria for the selection of individuals who show optimum adaptability to work in atmospheres with oxygen deficiency.

The physiological mechanism of adaptation is highly complex. It is known that processes promoting the formation and utilization of muscular energy are especially prominent in the organism of a trained athlete under great physical stress. Consequently, in training athletes for work under new environmental conditions, the reorganization of these processes becomes of great importance.

Many analysts still believe that glycolysis plays a leading role in the production of energy for high-stress muscular work, leading to an oxygen deficit and the accumulation of lactic acid. These concepts are contradicted by data /5 now available on the relations between the reactions of glycolysis and oxidation and on the energetics of these processes. Oxidation is much more powerful than glycolysis. It is also a more flexible and more variable source of energy. Calculations of the energy liberated in the glycolysis reactions, leading to the formation of the observed quantities of lactic acid in the human organism, show that this is only a small fraction of the total energy consumed by the athlete in performing his task. On the other hand, the energy of the oxidative reactions in which the oxygen taken up by the organism participates, is very close to the total quantity of energy expended on the work.

The energy produced by biological oxidation is of two main types: biological energy, stored in chemical phosphorus bonds, and thermal energy. The quantity of these two types of energy developed in the organism varies with the functional state of the organism. The rates of formation of thermal and biological energy and their ratio are subject to certain limits. These limits can be widened by training. Since the oxidative processes yield by far the greatest part of the body's energy, the possibility of training the systems that develop thermal and biological energy is of immense interest for the problem of adaptation of athletes to high-mountain conditions.

Research in the direction of widening the anaerobic productivity, i.e., glycolysis, seems less promising since this method of energy production is quantitatively negligible and is functionally subordinate to oxidation. /6

Biological oxidation takes place in the mitochondria, where it is accomplished in two ways, by free oxidation and by phosphorylation. Thermal energy is liberated at successive stages in the chain reaction of free oxidation. In the phosphorylation process, oxidation leads to the production of biological energy - phosphorylation. Depending on the degree of correlation, the quantitative relations between biological and thermal energy will vary. However, the total amount of energy liberated on oxidation of two hydrogen atoms to one molecule of water is constant.

Thus, the same quantity of oxygen taken up by the organism can provide for the production of various amounts of biological energy and, consequently, for the performance of varying amounts of work. Apparently, physical training gradually increases the correlation of oxidation and phosphorylation and also the yield of biological energy per unit oxygen assimilated by the body. Shifts take place, which are termed economization of oxygen utilization or economization of energetic processes.

We propose the following scheme of participation of oxidative processes in athletic training: When the body has become accustomed to systematic intense muscular work, all of its systems that provide for this work have been trained. Depending on the individual peculiarities of the organism and the character of the training, different systems will predominantly develop. The flow of biological energy can be intensified by increasing the supply of oxygen to the muscles or by increasing the correlation of biological and chemical energy, /7 in the total energy balance, i.e., the share of biological energy.

While it makes no difference, under lowland conditions, by which of these paths the top athletic form is reached, athletes having a high correlation of oxidation to phosphorylation will be advantageously situated under high-mountain conditions. This is the process that permits intense work under conditions of hypoxia.

In training athletes to compete under mountain conditions, in our opinion, attention should be focused on training the system of correlation of oxidation with phosphorylation, and on the selection of athletes in which this system is best developed. The development of a system of training and the selection of tests to determine the relative development of the linkage of oxidation with phosphorylation is a multidisciplinary task for physiologists, biochemists, and physical education instructors.

The proposed scheme of the participation of oxidative processes in intense muscular work and in the training of sportsmen is in complete accordance with present data on the biochemistry of oxidative and glycolytic processes. It is based on the data obtained in physiological and biochemical research on the functional capabilities of athletes, on athletic training and acclimatization to mountain conditions. It does, however, still require intensive and comprehensive experimental verification on animals and human subjects.

THE ROLE OF ANAEROBIC AND AEROBIC PROCESSES IN THE ENERGY SUPPLY FOR INTENSE MUSCULAR WORK /8

T.A.Allik
(Central Research Institute for Physical Culture, Moscow)

There are two reaction chains producing ATP* in the skeletal muscles, namely, glycolysis and oxidation. These chains are closely interrelated. Oxidation is the continuation of glycolysis, while glycolysis is the source of the substrate for oxidation. Other sources for this substrate are the conversions of fats and proteins.

Muscular work is performed over the intermediary of biological energy. The biological energy that can be produced in the chain of oxidative reactions is many times as great as in the chain of glycolytic reactions. The amount of biological energy produced in the oxidative chain may vary, owing to the equal and opposite changes in the production of thermal energy.

The quantitative relation between thermal and biological energy, produced in the oxidative chain, depends on how rapidly these two forms of energy are used up. When ATP, the carrier of biological energy, is removed from the medium, this ratio shifts toward greater production of biological energy. The number of ATP molecules may be as great as five for each atom of oxygen participating in the oxidation. In the organism as a whole, such conditions are established in extremely strenuous work. /9

During intense physical work, the content of lactic acid (LA) in the body may increase, leading to oxygen want. This has led to the idea that, under acute oxygen insufficiency, strenuous work is performed mainly by using the energy liberated in the glycolysis reactions, and that elimination of the oxygen debt reduces primarily to removal of the excess LA formed. According to this idea, the oxidative mechanism of biological energy production, which is considerably more powerful, is unable to function properly when the need for such energy is at a maximum.

Our calculations have been based on present data on the relation between oxidative and glycolytic processes, as well as on the changes in the oxygen consumption, oxygen deficiency, and energy consumed in muscular work described in the literature on the physiology of sports. These calculations showed that the biological energy produced during the course of glycolytic reactions is only a negligible fraction of the energy consumed in work. The energy liberated by oxidation, on the other hand, is quantitatively close to the total energy used in work. In the 100-meter dash, the energy produced by glycolysis is only 1/7 of the total energy used, while that produced by oxidation of reactions is about 6/7.

If we assume that most of the body's work in the 100-meter dash is in fact formed in the chain of glycolytic reactions, then to consume the accumulated /10

* ATP - adenosine triphosphate.

products of glycolysis by oxidation would take at least five times as much energy as is actually used during the dash.

These calculations show that the assumption of a significant role played by glycolysis in supplying the energy for intense muscular work cannot be confirmed, either by present biochemical data or by studies on the physiology and biochemistry of sports.

In our opinion, the phenomenon of the oxygen debt is explained by the existence of reserve sources of biological energy in the body. On the one hand, such oxygen reserves exist in hemoglobin and myoglobin. The blood oxygen level declines markedly during work. This induces the body to use a larger amount of oxygen than it receives from the air. After work has ended, this oxygen, borrowed from the blood and tissues, must be replenished to restore the level characteristic of the state of rest.

On the other hand, biological energy reserves exist also in phosphocreatine (PC). Some authors believe that PC is an anaerobic agent for the reduction of ATP. However, it must be recalled that PC is formed only from ATP. Consequently, PC is as much a product of oxidation or glycolysis as ATP itself. The participation of PC in the reduction of ATP has no effect on the ratio of aerobic to anaerobic sources of biological energy. It is possible that also other reserve sources of biological energy exist in the body.

The supply of energy for intense muscular work can be imagined to proceed as follows: During the first seconds of work, which is accomplished largely /11
with the energy of PC, the functions of all systems of the body are reorganized, and the rate of oxidative reactions increases. As a result of the oxygen consumption, the tissue oxygen level falls, and an increased flow of oxygen from the alveoli to the tissues begins. This mechanism acts like a suction pump. The oxygen level decreases not only in the tissues but also in the blood, and this the more so, the more rapidly oxygen is consumed. If respiration is unable to supply the requirements of the oxidative system, the blood oxygen level falls still further.

The oxidative processes can only proceed simultaneously with glycolysis, which is the source of the substrates for oxidation. Since, as the rate of oxidation rises the oxygen level of the muscular tissue falls, the oxidation reactions are retarded. The loss of oxygen in the sphere of oxidative reactions is compensated by the excess of substrates supplied by glycolysis, by the increased LA level. Thus, the excess of LA is not a sign of an accumulation of the end product of glycolysis - an accumulation adversely affecting work - but rather of an increase in the concentration of oxidation substrates which compensate for the loss of oxygen in the sphere of oxidative reactions and support the reaction rate required to maintain work. During restoration of the reserves exhausted by work, the LA level of the muscles decreases to normal. This process reflects the gradual slowdown of the oxidative reactions as the high-energy phosphorus /12
compounds (PC) are restored and the tissues become saturated with oxygen, and also indicates the consumption of the excess LA in the oxidative reactions.

The share of the anaerobic processes, i.e., of the glycolytic reactions, in the energy supply for intense muscular activity of man is slight. However,

urder these conditions, they are still the main source of the substrates for oxidation, so that the oxidative (aerobic) processes can proceed only simultaneously with the glycolytic (anaerobic) processes. The primary function of glycolysis in biological energy production can be compared with the operation of a pump which forces fuel under pressure into a powerful jet engine.

THE ANTIHYPOXIC ACTION OF THE NATURAL COMPOUND GLUCONO-DIMETHYLAMINO ACETATE (Pangamic Acid)

/13

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With the object of studying the regulating antihypoxic action of the widely distributed natural compound, gluconodimethylamino acetate (pangamic acid), A.V.Dokukin, Yu.S.Chechulin, Yu.V.Bukin, and A.I.Rode, of our laboratory staff, performed several series of experiments. The experimental animals were injected by the subcutaneous, intravenous, intracoronary, and subarachnoidal routes with pangamic acid, and given it in their drinking water (10-150-500 mg/kg); the survival time was observed under conditions of acute asphyxia on 245 white mice and 185 white rats in a hermetically sealed system, measuring the absorbed oxygen in ml/min. In the same environment, they measured the time of appearance of arrhythmia and fibrillation under the conditions of acute focal myocardial ischemia in 26 cats, and the time required for normalization of the heart biocurrents in four dogs.

The mean survival time of mice, given pangamic acid, was longer than that of the controls ($p = 0.06$); at the 20th minute from the start of the experiment, 9% of the controls and 3.3% of the experimental animals had died; at the 30th minute the figures were 66.5 and 56%, respectively. Rats given pangamic acid survived an average of 10 min longer than the controls.

Pangamic acid increases the resistance to hypoxia of healthy rats and of some rats in a state of acute streptococcal and staphylococcal intoxication. The volume of oxygen absorbed is inversely proportional to the survival time of the rat under the conditions of experimental hypoxia in a hermetically sealed /14 respirator system. The smaller the volume of oxygen absorbed by the animal, the longer it will survive and the more resistant it will be to hypoxia. The survival time is longer the younger the animal.

In cats given pangamic acid, arrhythmia set in 10.6 min after ligature of the aorta, and in the controls within 3.8 min ($p = 0.0124$); by the 20th minute after ligature of the descending branch of the left aorta, 69% of the controls and 20% of the experimental animals had died ($p = 0.05$). In dogs, pangamic acid temporarily eliminated (for 20 min) a ventricular extrasystole.

The positive regulatory effect of pangamic acid on the oxygen regime of the organism, under conditions of hypoxia, is attributed to the fact that this natural compound participates in the reactions of transmethylation as a donor of methyl groups. It stimulates methylation of nicotinamide in human subjects and oxidative demethylation. It increases the activity of tissue dehydrases, stimulates the function of the adrenal cortex, participates in the synthesis of choline, creatine, and perhaps also of adrenaline. It is well known that the

level of creatine phosphate in the myocardium and brain tissue falls sharply under conditions of hypoxia, which makes the intensification of creatine synthesis by pangamic acid particularly important.

PARTICIPATION OF ARTERIAL, VENOUS, AND TISSUE RECEPTORS IN THE REGULATION OF EXTERNAL RESPIRATION IN HYPOXIA /15

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Ever since the discovery of the chemoreceptors of the sinocarotid and cardioaortic regions there has been no doubt that the partial pressure of oxygen (pO_2) of the arterial blood is not only a means for regulation but also provides the afferent signals ensuring this regulation by reflex action on the respiratory center.

The following facts have been established:

1. Only the partial pressure of oxygen in the arterial blood constitutes an adequate stimulus of the chemoreceptors of these regions (but by no means the oxygen level).

2. After denervation of these zones, the minute volume (MV) does not increase when pO_2 in the arterial blood decreases.

3. Even after prolonged training in the altitude chamber, no other receptors replace the functions of the chemoreceptors of the cardioaortic and sinocarotid zones, although other adaptive reactions do persist.

A special study has shown that a low pO_2 does not stimulate the chemoreceptors; also in ischemic hypoxia of various organs, no reflex increase in the MV was noted. /16

Recently, reports have appeared on the regulatory effect of the lesser circulation on the MV in hypoxia. These reports are based on indirect comparisons of pO_2 in the mixed venous blood and the magnitude of the MV in human subjects, and on certain direct experimental data. Substantial discrepancies exist in the results and concepts of various authors on this subject. Today, there is no sufficient reason for assuming that the chemoreception of the lesser circulation has a major influence in the regulation of the MV.

Thus, only the significance of the chemoreceptors of the arterial system for the regulation of the external respiration during variations in the pO_2 and for maintenance of the relative constancy of the pO_2 in the arterial blood can today be considered as definitely proved. As shown by special studies, no adaptation of these receptors to oxygen insufficiency takes place, even under the protracted action of a decreased partial oxygen pressure. The specificity of these receptors is certain: They play a more important role in the regulation of respiration than in that of any other systems of the organism; no other

chemoreceptors induce such extensive changes in respiration.

In the complex regulatory system for the oxygen regime of the organism, various effector links (external respiration, cardiac activity, vascular tonus) not only play different roles in oxygen transport, but even have a different scheme of regulation. Since the function of external respiration in the /17 maintenance of oxygen transport is to ensure adequate oxygenation of the arterial blood, it is natural that the chemoreceptors, which regulate respiration in hypoxemia, should have been localized during the process of evolution only in the region of the major arteries.

FEATURES OF THE OXYGEN REGIME AND ITS REGULATION AT VARIOUS AGES /18

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1. Antenatal Period

Topics include: features of the change in oxygen regime in the pregnant organism, in connection with the pO_2 gradient required for adequate supply of oxygen to the developing embryo and fetus. Ability of the antenatal organism itself to regulate the oxygen regime. The effect of hypoxemia and hyperoxemia of the mother on the growth and development of the embryo and fetus. Physiological significance of the features of the oxygen regime during the antenatal period.

2. Postnatal Period

a) Period before adoption of a standing posture. - Topics include: Features of the oxygen regime (homeostasis) and its regulation in the period before adoption of a standing posture. Physiological significance of the high level of oxygen consumption during this period. Mechanisms (nervous and humoral) of regulation of the activity of the respiratory and cardiovascular systems to maintain the high level of oxygen consumption in this period. Causes of the /19 narrow range of potential lability of the respiratory and cardiovascular systems in the period before adoption of a standing posture.

b) Period after adoption of a standing posture. - Organization of rest and decreased oxygen consumption per unit body weight during rest. Role of the skeletal musculature in the mechanisms of organization of rest and decreased level of oxygen consumption (energy consumption) during growth and development of the organism. Mechanisms of gradual increase in potential lability of the respiratory and cardiovascular systems during growth and development of the body after adoption of the standing posture.

In connection with the data on relative ontogenesis obtained on rats, rabbits, and dogs (physiologically mature and immature), a comparative presentation of the values of the "energetic rule of the surface" and "energetic rule of the skeletal muscles" in the mechanisms of progressive decrease in oxygen consumption (energy consumption) in the state of rest during postnatal ontogenesis after adoption of standing posture. Physiological significance of the gradually decreasing level of oxygen consumption in the period after adoption of the standing posture. Role of the skeletal musculature in the mechanism of inhibition of the activity of the respiratory center and gradual decrease of the natural respiratory rate during postnatal ontogenesis. Decrease of the natural respiratory rate and concomitant decrease of the partial oxygen pressure in the

alveoli and in the blood. Significance of the resultant state of physiological hypoxemia in the mechanism of generation of vagal tonus (by stimulation of /20 the chemoreceptors of the sinocarotid and cardioaortic zones). Causes responsible for the high natural respiratory rate and absence of vagal tonus during the entire postnatal ontogenesis of idioadaptive (stenobiontic) organisms (especially in rats and rabbits), and lowering of the natural respiratory rate and appearance of vagal tonus in aromorphous or eurybiontic mammals.

These studies established the significance of systematic muscular training and training to hypoxia in rats and rabbits during postnatal ontogenesis as factors responsible for the stable decrease in the level of oxygen consumption (energy consumption), the natural respiratory rate, and the appearance of vagal tonus. The paper summarizes data from the research by V.D.Rozanova, S.I.Yenikeyeva, E.I.Arshavskaya, I.S.Ugolbayeva, D.U.Ermotova, O.T.Vatseva, and the author of this report.

SOME DATA ON THE OXYGEN CONSUMPTION OF THE FUNCTIONING HEART AND SKELETAL MUSCLES OF THE FROG

/21

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The musculus sartorius and heart of the frog are classical objects of physiological studies, and their investigation offers various advantages. Application of the polarographic technique permitted studying the respiration of these preparations under various experimental conditions. Our work yields the following conclusions:

The oxygen consumption of the frog heart may fluctuate from 20 to about 2500 μltr/gm of moist weight per hour, and is determined by the work done by the heart.

Adrenaline increases the oxygen consumption of the frog heart in proportion to the increase in the force of its contractions.

The respiration of the myocardium increases when damaged and rises sharply on its homogenization.

Adrenaline has no effect on the oxygen consumption of a homogenate of the myocardium and liver of the frog and rat.

The stimulating action of adrenaline on the oxygen consumption of the contracting heart of the frog is indirect, and is connected with the increase in the force of the contractions.

In experiments with perfusion of the frog heart in a closed cycle, the stimulating action of adrenaline on the function of the heart is not accompanied by an increase in respiration, even in cases where anaerobic processes of energy production are completely excluded.

The stimulating action of adrenaline on the work of the frog heart is not directly connected with a specific energetic process and is also observed /22 during the cardiac contraction under anaerobic conditions, even when glycolysis is stopped by monoiodoacetic acid.

The transition of the skeletal muscle of the frog from rest to contraction is accompanied by a 2 - 3 fold increase in its respiration, if the respiration of the muscle at rest is in the range from 30 to 100 μltr/gm/hr.

The respiration of the isolated m.sartorius of the frog at rest may be high, up to 500 μltr/gm/hr. One of the causes of this increase is the stretching of the muscle, its mechanical damage. The contraction of such muscles as a rule is not accompanied by a further increase in their respiration.

2,4-DNP (dinitrophenol) stimulates the respiration of a resting muscle with

a low oxygen consumption. It has less effect on the respiration of muscles with a higher oxygen consumption.

2,4-DNP has no effect on the respiration of the contracted frog muscle. The contractions of a muscle whose respiration at rest had been stimulated with 2,4-DNP are not accompanied by a further increase in respiration.

Adrenaline has no effect on the oxygen consumption of the isolated m.sartorius of the frog either at rest or during contraction.

ADAPTIVE CHANGES IN OXYGEN TRANSPORT IN THE BLOOD, CELLULAR PLASMA, AND MITOCHONDRIA /23

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The organism has an extraordinary ability to maintain the stability of tissue oxygen requirements at rest, and to vary it over a wide range during activity. To meet this requirement, the organism has extremely complex, delicately regulated and interrelated systems for oxygen transport: the system of pulmonary respiration, providing the required amount and the necessary partial oxygen pressure in the alveolar air; the cardiovascular system, carrying blood in the required volume and at an adequate rate; the blood, with its ability to pick up oxygen in the lungs and deliver it to the tissues; and, finally, the tissues themselves, in which the oxygen molecules travel over a complex path until, colliding with a stream of electrons, they acquire the ability to combine with ionized hydrogen, forming water, as the end product of biological oxidation. This latter process takes place in the mitochondria of the cells. Until then, no matter what compounds oxygen has formed, all are temporary and readily dissociate under certain conditions, being significant only as means of transport.

Necessary conditions for oxygen transport. It is generally known that the prime motive force of oxygen transport is diffusion, produced by the difference between the partial pressure of molecular oxygen at the hematopulmonary and hematohistological barriers. However, the transfer of the necessary amount of oxygen into the blood requires certain conditions, established by the peculi- /24
arities of hemodynamics and the properties of the blood itself.

In the tissues, molecular oxygen either diffuses directly into the mitochondria and there combines with cytochrome-oxidase (Cy-oxidase) or, as takes place in the muscular tissue, travels a complex route in the cytoplasm before entering the mitochondria. Since the muscular tissue accounts for 42% of the entire weight of the body, the features of oxygen transport are particularly important in the general balance of the oxygen supply of the organism. It is well known that muscular tissue is able to store oxygen in the form of a reversible compound with myoglobin ($My + O_2 \rightleftarrows MyO_2$), i.e., it is characterized by a certain oxygen capacity. The basic aspect of a combination of oxygen with myoglobin is determined by the character of the dissociation curve of oxymyoglobin.

The function of myoglobin is not only to deposit O_2 in the cytoplasm and to ensure the delivery of oxygen to the mitochondria when the direct diffusion of molecular oxygen becomes insufficient or stops altogether, for example, during systole or contraction of the skeletal musculature. The function of myoglobin also is to maintain the optimum diffusional gradient of the partial oxygen pressure between the capillary blood and the cellular cytoplasm, and between the cellular cytoplasm and the mitochondria, which the oxygen must directly reach in order to combine with the Cy-oxidase. Consequently, the function of myoglobin is to maintain the optimum conditions for the oxidative pro-

cesses.

In the mitochondria, molecular O_2 enters into reversible combination with/25 the Cy-oxidase; after liberation from the oxidase, the oxygen is ionized by the electrons transferred to it from the oxidase. It is only now that the oxygen becomes able to combine with ionized hydrogen atoms, i.e., with protons, to form water, which is the end product of biological oxidation. This ends the life cycle of molecular oxygen.

The process of terminal oxidation in itself is determined by various conditions. On the one hand, the reaction of oxygen with Cy-oxidase depends on the pO_2 of the medium. On the other hand, this reaction also depends on the activity of the cytochromal system, which supplies a flux of electrons to ionize the molecular oxygen. Finally, the rate of terminal oxidation is also linked with the activity of the enzymes that transport the protons (for instance, DPN-N and TPN-N). The maintenance of the oxygen regime of the organism is determined by the degree of balance between the rate of biological oxidation and the activity of the oxygen-transport systems.

Adaptive changes in the oxygen-transport systems. During the first period of changed environmental conditions, for example, when the organism enters a rarefied atmosphere, rapid reflex adaptive mechanisms go into action: The volume of pulmonary aeration increases; the minute volume of the lungs changes; a redistribution of blood takes place, maintaining intensified blood supply to the brain; the oxygen capacity of the blood increases, on account of redistributive erythrocytosis; the acid-base equilibrium of the blood is modified, en- /26 couraging greater dissociation of oxyhemoglobin; the decrease in pO_2 of the tissues facilitates passage of molecular oxygen from the capillary blood into the cellular cytoplasm.

Protracted duration of hypoxia will lead to an increase in erythropoiesis, i.e., an increase in the level of hemoglobin and the number of erythrocytes; the conditions for reaction between hemoglobin and oxygen are modified. As a result, the oxygen capacity of the blood increases and the conditions for transfer of oxygen from the capillary blood to the tissues are improved. The myoglobin content of the tissues rises, thus increasing their oxygen capacity and improving the conditions for the passage of oxygen from the blood into the cellular cytoplasm and from the cytoplasm into the mitochondria. In the mitochondria, the activity of Cy-oxidase and the hydrogen-transporting enzymes increases. As a result, the utilization of oxygen by the mitochondria proceeds at a high rate, despite the lower pO_2 in the medium, relative to normal conditions. The isolated tissues and the integral organism of an animal adapted to hypoxia increase their capability to draw oxygen from a medium with low pO_2, relative to that of an unadapted animal. Thus, maintenance of a normal or nearly normal oxygen regime of the organism is ensured under the new environmental conditions.

This picture probably occurs whenever the adaptation is not accompanied by a decrease in metabolism, and the oxidative metabolism remains at its former level, characteristic for the animal under its normal conditions of existence.

Matching the modifications in the oxygen-transport systems with the oxygen

requirements of the organism. For a normal healthy organism, the ability to /27
"match" the adaptive changes to the needs of the organism is characteristic. This is a kind of economy of adaptive reactions and is particularly distinct in adaptive changes in the transport properties of the blood. Experiments have shown a direct correlation between stimulation of erythropoiesis and initial oxygen capacity of the blood. The lower the initial hemoglobin level and the lower the number of erythrocytes in the blood, the greater will be the possible stimulation of erythro- and hemopoiesis. The oxygen capacity of the blood in hypoxia is in itself apparently determined by the intensity of the hypoxic stimulus, of course within certain limits. For an exact quantitative determination of the matching of the compensatory changes of the oxygen capacity of the blood and tissues to the oxygen requirements of the organism, the respiratory metabolism of the animals must be determined.

Regulation of the adaptive changes of the oxygen-transport systems. Under normal conditions, the linking of oxygen to the hemoglobin in the blood, the myoglobin in the muscles, and the Cy-oxidase in the cellular mitochondria, as well as the dissociation of these complexes, proceed according to the principle of dynamic automatic self-regulation. Certain prerequisites for this exist in the transport systems themselves. However, on disturbance of the oxygen regime of the organism, adaptive modifications of oxygen transport take place as a result of the regulatory influence of the nervous and humoral systems. Apparently, the mechanisms of these influences differ under the action of an acute and brief hypoxia and under the chronic influence of oxygen insufficiency. The /28
regulation of oxygen transfer in acute and chronic hypoxia have been studied, to various extents. Existing research data seem to indicate that both the nervous and humoral systems play a major role in the regulation of the adaptive changes of oxygen transport.

THE OXYGEN PRESSURE IN THE BRAIN IN VARIOUS PATHOLOGICAL STATES OF THE ORGANISM

/29

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and R.I.Mikhaylova
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The method of polarographic determination of the partial pressure of oxygen in the living brain has been used to establish the mode of change in oxygen absorption by the brain on any change in its functional state.

In a chrorological experiment, a considerable drop in oxygen pressure in the cerebral cortex was noted in traumatic shock, while in the erectile phase of shock, accompanied by a rise in arterial blood pressure, the oxygen pressure in the brain was higher than its initial value.

On ligation of the limb of an animal, exactly the same type of regular variations in oxyger absorption by the cerebral cortex is noted. Within a few minutes after application of the ligature, the oxygen consumption increases sharply, remairs high for 30 - 45 min, and then declines gradually. After removal of the ligature, an increase in oxygen consumption is noted, which takes several days to return to the physiological level.

The oxyger pressure decreases in the animal cerebral cortex, following a sirgle whole-body radiation dose of 1500 r of X-rays, while irradiation in divided doses, coming to a total of 1500 r, is not accompanied by a similar change in oxygen pressure. /30

In vitro tests on tissue respiration (by the Warburg method) showed that traumatic shock as well as whole-body irradiation sharply reduces the oxidative processes in the brain, and the processes of correlation between oxidation and phosphorylation are also affected.

In homogenates of the brain of animals, in the state of deep hypothermia, no disruption of correlation between oxidation and phosphorylation is noted. The warming up of the animals after extreme hypothermia leads to a rise in the oxidative processes and to their correlation with phosphorylation. If there are complications in the course of warming up, phosphorylation and its correlation with oxidation declines.

CONTRIBUTION TO THE MECHANISM OF ACTION OF OXYGEN ON THE ORGANISM UNDER NORMAL ATMOSPHERIC PRESSURE /31

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Physiology and clinical practice have collected reliable data on the changes in various body functions on inhalation of air with insufficient or excess oxygen. The discovery of the chemoceptive zones of the aorta and carotid region has been of great importance for the understanding of the mechanism of the complex shifts taking place in such cases. However, even today, much is still unknown about the action of oxygen on the respiration and the organism as a whole. In this connection, we made a series of studies whose results are given below.

Method. In comparative acute and chronic tests, we studied the following: state of external respiration (pneumography); reflex excitability of the respiratory center (from the excitation threshold of the vagus nerve exposed on a skin flap in the neck); oxygen pressure in the brain tissue, the myocardium, and in the cerebrospinal fluid (by the polarographic method); electric response of the respiratory muscles (electromyography); activity of the cardiovascular system (arterial pressure, ECG, heart mechanogram); state of the red blood (hemoglobin content, number of erythrocytes, hematocrit reading). The state of hypoxia was established by inhalation of air of reduced oxygen content and that of hyperoxia, by inhalation of oxygen at normal atmospheric pressure.

1. Changes in the oxygen content of the inspired air, both increase and decrease, were accompanied by a monotonous shift in the oxygen pressure in the /32 brain tissue, the myocardium, and the cerebrospinal fluid.

2. With intact innervation of the chemoceptive reflexogenous zones, O_2 inhalation leads to two-phase modifications in the external respiration: the first phase, a brief respiratory depression, gives way in 2 - 5 min to a phase of restoration of the respiration to the original level, in spite of the continued action of O_2. On inhalation of hypoxic mixtures, the external respiration is intensified.

3. The reflex excitability of the respiratory center shows shifts depending on the O_2 content of the inspired air (Table 1).

Moderate hypoxia (14 - 16% O_2) is accompanied by irregular fluctuations of the excitability of the respiratory center, both up and down. More extensive /33 hypoxia (9 - 14% O_2) leads in 70% of the experiments to a rise in the excitation threshold of the respiratory center; in the remaining experiments, excitability was either reduced or remained constant.

Conversely, inhalation of hyperoxic mixtures (30 - 80% O_2) usually led to a lower threshold of reflex excitability of the respiratory center.

4. After denervation of the chemoceptor aortic and carotid zones in the narcotized dog, inhalation of O_2 in a number of cases was accompanied by typical two-phase changes in respiration. This effect was more pronounced against the background of a preliminary inhalation of a hypoxic mixture.

TABLE 1

VARIATION OF THE THRESHOLD OF REFLEX EXCITABILITY OF THE RESPIRATORY CENTER ON INHALATION OF AIR WITH VARYING O_2 CONTENT

Oxygen Content in the Air of the Chamber, %	Number of Experiments	Threshold of Excitation of Respiratory Center		
		Higher	Unchanged	Lower
9 - 14	43	8	5	30
14 - 16	9	3	2	4
18 - 21	6	-	6	-
27 - 80	17	17	-	-

5. With intact innervation, hyperoxia induced two-phase changes in the biocurrents of the diaphragm: inhibition of inspiratory activity in the first phase, and gradual intensification in the second. This was accompanied by an increased frequency and amplitude of the biocurrents in the intercostal expiratory muscles, and by increased duration of the active phase.

The extent of changes in the electric activity of the respiratory muscles in hyperoxia was always greater after previous inhalation of a gas mixture with a lower O_2 content.

Inhalation of a hypoxic gas mixture led to an intensification of the biocurrents of the diaphragm and increased the frequency of its contraction; at the same time, the frequency, amplitude and duration of the active phase diminished in the expiratory intercostal muscles.

After complete denervation of both reflexogenous zones, hyperoxia in most cases induced increased diaphragm activity; the characteristic shifts in the activity of the intracostal expiratory muscles were not noted. Against the /34 background of a preceding hypoxia, the inhalation of oxygen by dogs with an interrupted chemoceptive innervation was accompanied by typical two-phase changes in the electric activity of the diaphragm observed with intact innervation.

The reaction to hypoxia after interruption of the aortic and sinocarotid zones was characterized by inhibition of electric activity in the diaphragm and intercostal muscles.

6. With intact innervation, oxygen inhalation induced a slowing of the rate of cardiac contraction and a persistent depression of arterial pressure, which lasted throughout the entire time of oxygen inhalation.

In the isolated heart, hyperoxia induced intensification of the myocardial contractions, while hypoxia decreased the contractile function of the myocardium.

7. The carbohydrate metabolism plays the dominant role in the mechanism of action of oxygen on the contractile function of the heart. The action of oxygen on the heart is intensified after an increase in the glucose concentration in the perfusion solution; on the other hand, depression of carbohydrate metabolism by addition of monoiodoacetate stops the activating influence of oxygen on the contractile function of the heart.

8. The changes in the red blood during hyperoxia were studied on two groups of 10 young healthy adults (athletes). The mean results of the experiments show that the first session of inhalation of pure oxygen leads to an increase in the erythrocyte count of the peripheral blood. In the following sessions, inhalation of oxygen produces hypoglobulia (in agreement with the data by Binet and Bocher, 1955).

The hypoglobulia is temporary, and the erythrocyte count gradually rises /35 within 30 min of oxygen inhalation (adaptation to hyperoxia).

Shifts in the blood hemoglobin level and in the hematocrit reading coincide with shifts in the erythrocyte count, thus making the results entirely reliable.

9. Determinations of the oxygen level in the cerebrospinal fluid of dogs showed that the oxygen content fluctuated from 0.17 to 0.30 vol.%, with an average of 0.23 vol.%.

Inhalation of 96% oxygen induces a rise in the partial pressure of oxygen in the cerebrospinal fluid; an inhalation of hypoxic mixtures reduces the pO_2 in the cerebrospinal fluid. These shifts in O_2 pressure of the fluid are gradual, and the latent period for the change of pO_2 in the fluid is 3 - 4 times as long as in the brain tissue and blood.

Vagotomy and denervation of the sinocarotid reflexogenous zones leads to a considerable retardation of the shifts in the oxygen pressure of the cerebrospinal fluid. This permits the hypothesis that the permeability of the hematoencephalic barrier depends on innervational influences.

The changes in the external respiration on inhalation of hypoxic and hyperoxic mixtures coincide in time with the shifts of pO_2 in the brain tissues and blood; the shifts of pO_2 in the cerebrospinal fluid lag far behind those in the respiration. Therefore, the shifts in the pO_2 of the cerebrospinal fluid, which is closely connected with the fourth ventricle of the brain, cannot be regarded as responsible for the changes in respiration during shifts in the gas composition of the blood.

10. Our data permit to distinguish direct and reflex action of oxygen on the organs and tissues. Under normal atmospheric pressure, an increase in the

O_2 level of the blood (or of the nutrient liquid) causes an intensification of/36 respiration even in the isolated heart; a decrease in oxygen level to a depression of function. With intact innervation, a shift in the oxygen content of the inspired air results in compensatory reactions tending toward maintenance of a constant blood oxygen level and its constant supply to the tissues.

These reactions are mediated by the chemoreceptors and lead to coordinated shifts in the activity of the respiratory, circulatory, and blood systems. These three systems should be regarded as a single interrelated system for supplying oxygen to the organism. The resultant index of the combined activity of all parts of the system is the pO_2 of the blood and tissues.

By virtue of this, the isolated study of the shifts taking place in any one of these systems is insufficient and cannot give a complete idea on the mechanism of the changes taking place in the organism as a whole, under conditions of hypoxia ard hyperoxia.

MATHEMATICAL APPROACH TO THE STUDY OF THE DYNAMICS OF HUMAN ENERGY CONSUMPTION IN A CLOSED SYSTEM

/37

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The investigation of human energy consumption by the calorimetric method or by determining the composition of the atmosphere in a sealed chamber gives only a generalized idea, but does not reveal the dynamics of the characteristics under study, owing to the great inertia of the system of chamber plus analyzer.

The conventional methods of a dynamic study of energy consumption from the respiratory metabolism involves the use of mouthpieces or masks, which in itself limits the length of the recording.

The authors propose a mathematical approach which, by using certain methods of the theory of automatic control, not only determines the integral indices of gas exchange in a closed chamber, but also discloses the slope of the characteristics of interest during the entire period.

The method is based on the unique relationship between the influence (change in human respiratory metabolism) exerted on a dynamic system (chamber plus devices for stabilizing the parameters of the physical medium in the chamber) and the reaction of the system (variation of the parameters of the physical medium).

A determination of the dynamics of gas exchange is based on the solution of an integral equation, relating the formula for any parameter of the physical medium in the chamber to the characteristics under study, provided that the dynamic properties of the system are known. As an illustration, the authors describe a chamber with controlled flow ventilation in which predetermined conditions for the medium are automatically maintained. The course of oxygen con- /38
sumption is considered as the characteristic to be studied.

The method permits the use of a digital computer for solving the integral equation, considerably shortening the work-up of the data.

OXYGEN EXCHANGE AT INTENSE MUSCULAR ACTIVITY IN MAN /39

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The level of oxygen consumption in the human being, registered from the indices of pulmonary gas exchange, increases by a factor of 10 - 20 during intense muscular work (Dill, 1936; Robinson et al., 1939; Ostrand, 1955; Yefremov, 1949, and others). The rate of oxygen consumption in the working skeletal muscles may increase by a factor of 100 at the same time (Assmussen, Nielsen, Christensen, 1939). The study of the physiological mechanisms that regulate the rate of oxygen consumption during strenuous muscular activity are important for a correct understanding of the features of energy exchange in man, under normal and pathological conditions.

Among the well-known factors of cellular metabolism, the following two factors have the greatest influence on the rate of oxygen utilization in the tissues during muscular work: a) the formation, during muscular contraction, of free amounts of ATP capable of effecting "respiratory control" in the mitochondria; b) the formation, during the reactions of dehydrogenation of energy sources (carbohydrates and fats), of metabolites which serve as the starting substrates for further oxidative transformations. The rate of dissociation of ATP during muscular contraction, like the rate of formation of the substrates of aerobic oxidation, is linearly related to the degree of stress. According to available data (Chires et al., 1956, 1959; Sekevich, 1959; Carlson, 1963; Hess, 1963) /40 the division of the total metabolic space into individual phases interconnected by the diffusion of the intermediate metabolites, as well as the competition between glycolysis and respiration for the general substrates and cofactors, exerts a substartial influence on the character and degree of oxygen exchange in the tissues.

Based on the above facts, we developed a kinetic model of oxygen exchange in the human organism, which assumed the existence of intracellular or intraorganism compartmentalization of the processes of aerobic exchange, and the linear dependence of the rate of these processes on the production of ATP in muscular activity. For those cases of muscular activity in which the entire cycle of oxidative transformations is completely localized within the muscle cell, the solution of the fundamental equation of kinetics derived on the basis of the proposed model, leads to the single-component exponential curve of the increase in oxygen consumption during muscular work:

$$ {}_{E}\dot{V}_{O_2}^{t} = {}_{E}\dot{V}_{O_2}^{\infty}\left(1 - e^{-K \cdot t}\right) \qquad (1) $$

where ${}_{E}\dot{V}_{O_2}^{t}$ is the rate of oxygen consumption at any given time t after the beginning of the effort (subtracting the value of oxygen consumption during rest); ${}_{E}\dot{V}_{O_2}^{\infty}$ is the level of oxygen consumption in the stationary regime of work; k is

the rate constant of oxygen consumption during work; t the time of work; and e is the base of natural logarithm. For cases of muscular work involving the formation of oxidative substrates able to diffuse between the phases of meta- /41
bolic space, the solution of the corresponding system of differential equations leads to the two-component exponential expression for the curve of oxygen consumption:

$$ {}_{E}\dot{V}_{O_2}^{t} = {}_{E}\dot{V}_{O_2}^{1}\left(1-e^{-k_1 \cdot t}\right) + {}_{E}\dot{V}_{O_2}^{2}\left(1-e^{-k_2 \cdot t}\right), \qquad (2) $$

where ${}_{E}\dot{V}_{O_2}^{t}$ is the level of the stationary regime of oxygen consumption for intramuscular oxidative transformations; ${}_{E}\dot{V}_{O_2}^{2}$ is the level of the stationary regime of oxygen consumption for oxidation of the diffusing metabolites in the various phases of metabolic space; k_1 and k_2 are the rate constants for the respective fractions of oxygen consumption.

To describe the curve of oxygen consumption during the period of recovery after muscular work, the following solutions are valid for the differential equation derived from this kinetic model of oxygen exchange:

1. For the case when the entire cycle of oxidative transformation is completed within the muscle itself:

$$ {}_{R}\dot{V}_{O_2}^{t} = {}_{R}\dot{V}_{O_2}^{o} \cdot e^{-k' \cdot t} \qquad (3) $$

where ${}_{R}\dot{V}_{O_2}^{t}$ is the level of oxygen consumption at any time t after the end of the work (subtracting the value of the oxygen consumption at rest); ${}_{R}\dot{V}_{O_2}^{o}$ is the level of oxygen consumption at the initial time of the recovery period (this level equals $\dot{V}_{O_2}^{t}$ at the end of work); k' is the rate constant of oxygen consumption during recovery; t is the time of recovery.

2. For the case where metabolites able to diffuse between the phases are formed during the exertion:

$$ {}_{R}\dot{V}_{O_2}^{t} = {}_{R}\dot{V}_{O_2}^{1} \cdot e^{-k_1' \cdot t} + {}_{R}\dot{V}_{O_2}^{2} \cdot e^{-k_2' \cdot t} \qquad (4) $$

where ${}_{R}\dot{V}_{O_2}^{1}$ is the level of oxygen consumption at the beginning of recovery (at /42
the end of work), corresponding to the oxidation of the metabolites that had completed the full cycle of transformation within the working muscles; ${}_{R}\dot{V}_{O_2}^{2}$ is the level of oxygen consumption at the beginning of restoration, which corresponds to the oxidative elimination of the metabolites that have diffused between the phases of metabolic space; k_1' and k_2' are the rate constants for the component fractions of oxygen consumption during the period of recovery.

According to most present data (Barr, Himwich, 1926; London, 1932; Edwards, 1934; Henry, 1956), the most suitable candidate for the role of oxidative substrate able to diffuse between the phases of metabolic space is lactic acid, which is formed during the glycolytic reduction of oxides. If we assume that the oxidation of the quantity of lactic acid formed during work is identical with that fraction of the working and recovery oxygen consumption which is de-

scribed by the expression for a diffusing metabolite, then the designation of this fraction of oxygen consumption as "lactate" oxidation by Marguerie et al. (1933) appears ertirely justified. The other fraction of oxygen consumption, not connected with the oxidation of lactic acid, will be termed "alactic" oxygen consumption.

With the object of experimental verification of the proposed kinetic model of oxygen exchange in the human organism during muscular activity, we made special studies in which the oxygen consumption during work and recovery was measured continuously, and blood samples for determination of the lactic acid /43 level were also taken continuously.

Isometric exercises, running, or work on the bicycle ergometer, at three different output levels, moderate, severe and exhausting, were used as the test stress. Moderate stresses were considered to be exercises in which no marked lactic acid formation was observed; at the end of the exercise the blood lactic acid level did not exceed 20 - 30 mg%. The severe stresses included those types of work in which formation of lactic acid up to 120 - 130 mg% was observed. Exhausting stresses involved extremely high accumulation of lactic acid in the blood, as a rule over 200 mg%. The time of such exercise was usually limited to 2 - 3 min.

On performing the moderate exercise, the oxygen consumption curve during work and recovery exactly follows the one-component exponential relation, which is in satisfactory agreement with the one-phase character of oxidative conversions ir the working muscles, postulated in the kinetic model. Under these conditions, the rate constant of oxygen consumption during work does not vary with increasing output level of the work, but the rate constant of oxygen consumption during recovery is progressively slowed with increasing load. The rate constant of working oxygen consumption for moderate exercise is 6 - 14% greater than the corresponding value of the rate constant of replenishing the oxygen deficit. No extensive correlation seems to exist between the level of the stationary regime of oxygen consumption and the rate constant of oxygen consumption during moderate exercise.

The rate curve of oxygen consumption during strenuous exercise is distinctly separated into two phases. The parameters of the second, slow, component /44 of oxygen consumption during work and recovery are closely linked with the corresponding kinetic indices of the blood lactic acid level, thus permitting identification of the slow component with the lactate oxygen consumption. The rate constant of lactate oxygen consumption during work is 3 - 6 times as slow as that of alactate oxygen consumption; during replenishing of the oxygen deficit, the difference between these constants may reach a factor of 30 - 50. With increasing strenuousness of the exercise, the rate constant of alactate oxygen consumption during work increases in the same way as during moderate exercise; the constant of lactate oxygen consumption during work at first likewise increases with increasing intensity of exertion, but then begins to drop rapidly. During the recovery period after heavy exercise, both constants show a slowing with increasing stress. There is a positive correlation between the level of the stationary regime of oxygen consumption and the rate constant of alactate oxygen consumption during work, but this correlation is absent for the rate constant of working lactate oxygen consumption, and for both constants during the

recovery period.

In exhausting exercise, despite the accumulation of considerable amounts of lactic acid in the working muscles, the curve of working oxygen consumption no longer contains two components; the kinetics of oxygen consumption is here characterized by only a single rate constant. This rate constant increases with severity of the exercise, but at minimum intensity of this type of stress it /45 is three times as slow as the constant of alactate oxygen consumption at the maximum load, where the curve does separate into two components. During the recovery period after exhausting exercise, as in the case of strenuous exercise, the oxygen consumption curve is distinctly separated into two phases. The rate of replenishing of the slow fraction of the oxygen deficit exactly reflects the value for the kinetic constants of the curve of lactic acid elimination. In exhausting exercise, the rate constant of lactate oxygen consumption shows a positive correlation with the individual maximum of oxygen consumption.

The above-discussed regularities in the variations of the kinetic parameters of the oxygen consumption curve in strenuous muscular work can be explained by the known laws on the regulatory interrelations of the processes of aerobic and anaerobic cellular exchange, and by the features of the circulatory shifts at extreme muscular stress.

INFLUENCE OF VARIATION IN THE MYOCARDIAL OXYGEN PRESSURE ON THE CONTRACTILE FUNCTION OF THE MYOCARDIUM IN RESPIRATION UNDER EXCESS PRESSURE

/46

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In acute experiments on dogs made to inhale oxygen under excess pressure we simultaneously recorded: pO_2 of the myocardium by the polarographic method, the coronary blood flow according to Neuens, the kinetocardiogram (KCG), the seismocardiogram (SCG), the electrocardiogram (ECG), the arterial pressure in the carotid artery (AP), and the pneumogram.

On respiration under excess pressure of 200 mm w.c., the pO_2 of the myocardium increases or decreases during the first 20 - 30 sec (first phase). The amplitude of the elements of the KCG and SCG decreases. This decrease is more rapid than the fluctuation of the curve on the polarogram and in time approaches the decrease in the coronary blood flow.

Respiration under excess pressure of 400 mm w.c. in the first phase is always accompanied by a decrease in myocardial pO_2. The decrease in the rate of the coronary flow and in the amplitude of the elements of the KCG and SCG is more pronounced. The resultant contraction of the mechanical systole relative to the electric systole, together with the considerable decrease in the pulse pressure, can be evaluated as signs of the decrease in the contractile power of the myocardium.

At good adaptation to respiration under excess pressure, phase II sets in within 20 - 30 sec. During this phase, there is a partial recovery in the /47
level of coronary flow and, to a slightly lesser extent, of the myocardial pO_2. The amplitude of the elements of the KCG and SCG increases above the original level. The increase in amplitude of the first sound in most of the experiments is parallel to the coronary flow.

Analyses of the indices of the polarogram, the coronary flow, the SCG, KCG, ECG, AP, and pneumogram permit postulating that the reason for the partial recovery of the contractile function of the myocardium in phase II of respiration under excess pressure, together with the increase in coronary flow may likewise lie in the increased oxygen consumption by the heart muscle.

Soon after phase II, in respiration under still greater excess pressure, phase III sets in. This phase is characterized by a brief stabilization of the polarogram, followed by an undulating decline. This is accompanied by a progressive decrease in the amplitude of the KCG and SCG.

On transition to respiration under normal pressure, the myocardial pO_2 and the coronary flow increase above the original level and gradually return to normal. The sharp respiratory arrhythmia of the heart is accompanied by an al-

ternation of cardiac cycles, with high and low kinemia. The sense of the amplitudes of both SCG and KCG, during this period, is usually in opposite directions.

MOTOR HYPOXIA /48

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In this paper, on the basis of many years of personal research and of literature data, an attempt is made to settle the question of hypoxic states during muscular work, their variation with increase in athletic training, and the adaptation of athletes to hypoxia under stressed (repeated) exertion.

The data obtained in this research disclosed a number of features, which essentially differentiate motor hypoxia from other hypoxic states. Motor hypoxia arises primarily under normal atmospheric pressure in healthy subjects, for example, in trained athletes, and to an extent that is greater the greater the degree of training and the greater the physical fitness. This disorder is created at elevated oxygen consumption and is only relative, since the insufficient oxyger supply during work takes place only relative to the instantaneous oxygen demand. The simultaneous hypercapnia has an important adaptive significance. A characteristic feature of motor hypoxia is the possibility of "controlling" it during voluntary motion, and of fixing the magnitude of the hypoxic shifts desired and the time of their action. This permits the use of motor hypoxia as a natural stimulus to cause progressive changes in the organism, leading to an expansion of the functional capabilities of the organism and help /49 in overcoming fatigue.

Various modifications of the methods of bloodless oxyhemography, in combination with the method of gas analysis and other methods, during high and prolonged laboratory stresses and certain athletic stresses, made it possible to establish marked arterial hypoxemia (12 - 16% or more below initial level) and in many experiments also a distinct excess of post-exercise respiratory metabolism over its level during work.

A number of conditions of muscular work, characteristic of modern athletic training, were simulated by us in the laboratory (for example, using the restriction of pulmonary aeration, etc., characteristic for various forms of motion) and also in experiments under conditions close to those of natural training. We studied high-stress work on the exercise bike, simulated diving, heavy exertion in 500-m swimming under water in a scuba outfit, complex muscular activity on gymnastic exercisers, etc.

Experiments in determining the partial oxygen pressure in the alveolar air during development of motor hypoxemia have shown almost complete agreement as to the extent of hypoxemia with the decrease in partial oxygen pressure, in accordance with the classical ratio expressed in the Barcroft curve on the characteristics of concomitant hypercapnia. In a series of experiments on particularly strenuous and prolonged work, the hypoxemic shift exceeded by several percent the value corresponding to the partial oxygen pressure in the alveolar /50 air. An artificial increase in aeration and inhalation of pure oxygen did not

eliminate this hypoxemia, which indicates the considerable significance of arteriovenous anastomosis in the lesser circulation, which facilitates the work of the right heart. The higher the degree of training of the athletes and the more work they had done, the more pronounced was their hypoxemia. In untrained subjects, even minor hypoxemic shifts had a sharp effect on various aspects of motor activity (the differences were statistically substantiated), while considerably greater hypoxemic shifts in trained athletes caused only slight changes in motor activity (the shifts were not statistically reliable).

Systematic athletic training, under ordinary conditions at sea level, leads to a high degree of adaptation to hypoxia, which records well in extreme hypoxic tests comprising retention of breath, respiration in a closed space, inhalation of a gas mixture with a low partial oxygen pressure, and so on. Athletes trained under prolonged and excessive stress showed the highest degree of adaptation to hypoxia. They exhibited substantial differences in this respect, depending on the stage of training: the more advanced this stage, the more pronounced was their adaptation to hypoxia (the differences were statistically reliable).

Oxygen insufficiency is primarily correlated with the degree of strain of the muscular functions, and with the frequency and level of the stress. In many cases (for not very strenuous work and free respiration), no arterial hypoxemia takes place; here, an oxygen deficit occurs after the end of the work, /51 in the form of regional hypoxemic shifts, which variously interact during the course of work, both in time and in the size of the shifts, creating a dynamic "mosaic" of hypoxemic processes in various parts of the body.

A substantial oxygen deficit is created in relative hypoventilation connected with some forms of motor activity. The more strenuous the work and the longer its duration, the greater will be the effect on the magnitude of the hypoxemic shift by even a brief (2 - 3 sec) holding of the breath, or a brief restriction of pulmonary aeration.

Obviously, changes in the lesser circulation and biochemical shifts in the blood and the working muscles have a major influence on the appearance of hypoxemic shifts in muscular work.

The author gives his opinion on the possible physiological mechanism of motor hypoxia and considers certain aspects of the regulation of oxygen exchange during voluntary human motor activity.

POSSIBLE MECHANISMS OF LOWERING OF THE BRAIN METABOLISM IN OXYGEN WANT OF THE ORGANISM

/52

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It is well known that if the oxygen supply to the brain tissue is insufficient, the phospholipide metabolism is lowered. It was of interest to analyze the mechanism of this lowering under general oxygen want of the organism.

White rats were placed for two hours in an altitude chamber, in which the pressure was reduced to 240 or 180 mm Hg. The rate of the phospholipide metabolism of the cerebral cortex was judged from the rate of incorporation of radioactive inorganic phosphate, measured by the relative specific radioactivity (RSR) of the phosphorus of the total phospholipides of the brain tissue.

A simulated altitude of 240 mm Hg induced a 31% drop in the RSR of the phospholipides, and a drop of 53% at a vacuum of 180 mm Hg. The rectal temperature fell 5.2° and 10.1°C, respectively. Since it is well known that hypothermia in itself, even at atmospheric pressure, depresses a number of metabolic processes in the brain tissue, the question arises as to what extent this decrease in the phospholipide metabolism of the brain was due to the oxygen want of the brain tissue resulting from the low oxygen content of the surrounding medium, and to what extent it was merely due to hypoxia accompanying the hypothermia.

If the body temperature of rats in the altitude chamber at 240 mm Hg was held at the normal level by artificial heating, no decrease in the metabolic /53 rate was observed, but the mortality rate of the rats in the altitude chamber increased sharply. On the other hand, when rats at the same pressure were artificially cooled, causing an average drop of 13.3°C in rectal temperature, a greater lowering of the phospholipide metabolism in the brain (by 64.5%) resulted.

A comparison of all results showed: First, at equal barometric pressure, the decline in the phospholipide metabolism of the brain depends on the depression of the rectal temperature; second, at the same depression of rectal temperature, the RSR of the brain phospholipides of rats, kept at various barometric pressures, was the same. An analysis of the data scattering suggests that the RSR of the brain phospholipides in rats, subjected to a lower barometric pressure, depends with statistical reliability ($P < 0.05$) on the body temperature of the arimal and is independent of the partial oxygen pressure in the surrounding medium.

The immediate cause of the depression in the metabolism of the brain phospholipides in oxygen want of the organism apparently is not so much the decrease in the partial oxygen pressure in the brain tissue itself as the drop in blood temperature and thus also of the brain temperature. Presumably, this hypo-

thermia, induced by the oxygen want of the organism, is the basic factor in the depression of the biochemical systems responsible for the synthesis of phospholipides.

The sharp rise in the mortality rate of animals under reduced barometric pressure, when the body temperature was artificially maintained at the normal /54 level, gives grounds for the assumption that the hypothermia induced by oxygen want of the organism is of a protective, adaptive nature.

REGULATION OF TISSUE OXYGENATION BY ERYTHROCYTES /55

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The regulation of oxygen release by the erythrocytes plays an important role in the regulation of the oxygen regime of the body (the uptake of oxygen by erythrocytes in the lungs usually requires no regulation in view of its exceedingly high rate). The problem is essentially that of increasing the percentage of oxygen given up in the capillaries, making it possible to maintain a high partial oxygen pressure over a rather long segment of the capillary, a result thus equivalent to increasing the supply of oxygen to the tissues, in replacement of inspiration of additional oxygen.

As far back as the Thirties, we and our associates were able to demonstrate that glycolysis in erythrocytes is a powerful activator of their release of oxygen, attributable primarily to the decrease in their pH. A lowering of the pH of the "plasma", at simultaneous glycolysis in the erythrocytes, will not accelerate the release of O_2 by the erythrocytes, but rather will decrease it because of the simultaneous reduction of glycolysis.

We also showed that the extent of glycolysis in the erythrocytes (hemoglycolysis) is subject to the influence of several hormones (confirming the literature data in part and contradicting them in part): injections of insulin, cortin, and cortisone increase hemoglycolysis, while injections of adrenaline decrease it. Therefore, it must be assumed that the release of O_2 by the erythrocytes is regulated by the neuroendocrine system. It is possible to improve the O_2 release by the erythrocytes over the intermediary of hormones or by intensifying the function of the respective endocrine glands. This is accomplished, for /56 the insular apparatus and the cortex of the adrenals, by physical training.

According to preliminary data, the decomposition of bicarbonates by the carboanhydrase of the erythrocytes intensifies their oxygen release, which apparently can be explained by the release of CO_2 from the bicarbonate. Results obtained by us as long ago as 1937 suggest the participation of carboanhydrase in the dissociation of oxyhemoglobin. This was later confirmed by other authors.

In still uncomplete experiments, we found that the action of cold, in the form of a shower or bath, markedly increases the intensity of hemoglycolysis. Apparently, this action is also mediated by the neuroendocrine system.

A shift in the dissociation curve of oxyhemoglobin to the right (intensified oxygen output), as indicated in the literature, seems to be produced by compounds such as the reduced glutathione of the erythrocytes and by ascorbic acid.

Our own findings, and data obtained in collaboration with M.M.Mirrakhimov

and his coworkers, indicate that several vitamins of the B group act favorably on the factors intensifying oxygen release by erythrocytes. Thus, nicotinic acid increases hemoglycolysis in experiments; in clinical practice, intravenous injection increases not only the hemoglycolysis but also raises the level of reduced glutathione and alkaline reserve of the blood.

Injections of vitamin B_{12} have the same effect. The blood hemoglobin level falls which, according to our data, does not mean an increased fluidity of the blood but rather the transfer of some of the erythrocytes into reserves of the organism, due to an increase of the oxygen-releasing capability of each individual erythrocyte.

Injections of pyridoxine and thiamine, as well as the use of diathermy in the region of the solar plexus, increased the energy of hemoglycolysis in /57
patients. Thiamine exerts a similar influence, not only in injections but also in experiments.

According to our data, hemoglycolysis and its products such as lactic and pyruvic acids (in the form of the sodium salts) increase the dehydrating function of the carboanhydrase of the erythrocytes, suggesting an intimate correlation between glycolysis and the function of carboanhydrase. By forming the anions of lactic and pyruvic acids, hemoglycolysis apparently establishes the optimum conditions for the function of carboanhydrase, which thus participates not only in the oxygen but also in the CO_2 exchange. Thus, lactic and pyruvic acids play a dual role: Their hydrogen ions intensify the dissociation of oxyhemoglobin, while their anions intensify the activity of the dehydrating function of carboanhydrase.

Intravenous injection of glucose leads to an intensification of hemoglycolysis, so that one could regard glucose therapy as an oxygen therapy.

Thus, we have found a considerable number of factors with favorable action - regulation and control - on the oxygen regime of the body, intensifying the oxygen release by erythrocytes in the capillaries. All constitute means of prophylaxis and control of hypoxia (of course, with the exception of its histotoxic form).

In dogs, at various elevations above sea level, hemoglycolysis plays a definite role in the biochemical mechanisms of adaptation to the high mountains, i.e., increasing the energy of the animal body. The concentration of reduced glutathione is also increased at 3200 m above sea level, confirming the results of N.N.Sirotina and other authors.

CONTRIBUTION TO THE QUESTION OF THE METHODS OF MEASURING THE MAXIMUM OXYGEN CONSUMPTION

/58

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The determination of the physical fitness of athletes has long been of interest to researchers in the physiology and medicine of sports. Measurements of the maximum oxygen consumption (MOC) during extreme stress, depending on the functional state of the so-called "oxygen system" of the human organism, are widely used for this purpose.

The basic feature of many of the described methods of determining the MOC is the one-gas analysis of the air exhaled during exercise. The methods differ in the procedure used to overcome the functional inertia of the individual components of the "oxygen system", and also in the character and duration of the physical exercise.

In this paper, we are giving experimental data on MOC, which were not determined at the time of extreme stress but immediately after it, during a 30-sec period of oxygen recovery.

The subjects were top athletes, members of the USSR swimming team at the Tokyo Olympic Games of October 1964 (see Table 1).

The Table indicates that the MOC of the female athletes reached four liters of oxygen per minute, and that of the boys over six liters. The highest values were not obtained during work on the bicycle ergometer but after four 50-meter swims, with 15-sec rest periods.

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However, it is not the absolute values of the MOC that are of greatest interest but their values per kilogram of body weight, since in some cases low absolute values of the MOC give higher values for the oxygen consumption per kilogram of weight.

Conclusions

1. The most complete mobilization of all components of the "oxygen system" of athletes is attained in physical exercises that are specific, relative to coordination structure and work of extreme intensity.

2. Functional shifts of extreme intensity of the principal components of the "oxygen system" are maintained for 30 sec of the oxygen recovery period.

3. It may be that the specific physical exercises activate the utilization

of oxygen by the muscle tissue because of optimum mobilization - under given conditions - of the functions of oxygen exchange in the entire system that regulates the consumption of oxygen in the body.

TABLE 1 /60

MAXIMUM OXYGEN CONSUMPTION OF SWIMMERS, MEMBERS OF THE USSR SWIMMING TEAM (MEASURED BY TWO METHODS)

Name	Date of Birth	MOC during Work on Veloergometer		MOC within 30 sec after 4×50 Meter Laps	
		absolute	per kg	absolute	per kg
Boys					
Karetnikov	1942	4.857	61.481	6.169	72.290
Safronov	1944	5.018	72.509	4.899	72.90
Berezin	1941	4.534	56.322	6.173	76.683
Kreys	1944	4.164	56.349	5.670	74.117
Tutakayev	1943			5.19	77.462
Prokopenko	1937			6.219	83.480
Fotin	1945	5.611	67.368	6.369	78.629
Paramonov	1942	3.396	49.217	6.295	90.706
Semchenkov				5.920	67.70
Mazanov				4.770	68.826
Girls					
Devyatova	1948			4.390	73.200
Babanina	1943	3.986	59.670	4.224	65.00
Bystrova	1947	3.253	49.132	3.380	52.800

CORTICO-SUBCORTICAL INTERRELATIONS IN HYPOXIA /61

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The effect of brief hypoxia on the electric activity of the sensorimotor, parietal, temporal and occipital cortex, the substantia reticularis of the mesencephalon, and on various nuclei of the thalamus, hypothalamus and hippocampus, was studied in acute experiments on narcotized rabbits. As the electroencephalogram (EEG) index of activity of these structures, we selected the first appearance of the slow regular rhythm, 4 - 7 per sec, which according to A.N.Shumilina (1958, 1959) characterizes the state of stress of the organism set up during biologically unfavorable reactions.

It was shown that brief inhalation of a hypoxic mixture (7.5% O_2 in N_2) induces, in all investigated structures, an EEG reaction of activation, namely, the appearance of the slow regular rhythm 4 - 7 per sec. The reaction of activation is registered primarily in the subcortical structures, first in the reticular formation of the mesencephalon and then, after 0.5 - 3 sec, in the cerebral cortex. These data permit the conclusion that the mesencephalic reticular formation plays a dominant role in the reaction of the central nervous system to hypoxia.

The deeper hypoxia caused by the inhalation of a mixture containing 5% of /62 O_2 and N_2 (under normal pressure of CO_2) is characterized by the appearance of slow, high-amplitude, polymorphous EEG waves which are most distinctly and sharply expressed in the cerebral cortex.

In the thalamus and reticular structures they are less distinct. These data confirm the generally accepted view that the cerebral cortex is the most susceptible to depressive influences in deep hypoxia.

In the second series of experiments we compared the reaction to hypoxia with that to a painful stimulus under the conditions of amirase action. We found that the activation reaction to hypoxia persists after cessation of activation and response to pain. This means that the hypoxic reaction is not blocked by aminase, or is blocked considerably less than the pain reaction. These data seem to indicate that the reaction to hypoxia and the pain reaction, which have almost the same manifestation, are in fact completely different in biological quality and evidently use different paths of excitation in the central nervous system.

SOME MECHANISMS OF REGULATION OF THE RESPIRATORY SURFACE OF THE BLOOD IN CONNECTION WITH OXYGEN INSUFFICIENCY

/63

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The increase in the respiratory surface of the blood on account of the increase in the number of erythrocytes is well known and is an important factor in the adaptation of the organism to the conditions of oxygen insufficiency. According to present data, the decrease in the partial oxygen pressure stimulates the activity of the blood system, mediated by complex neurohumoral mechanisms. In particular, under the action of acute hypoxia, the most important factor is considered to be the reflex mechanism of erythrocyte redistribution, the afferent part of which comprises the chemoreceptors of the carotid sinuses, while the efferent part (effector) is the spleen. The participation of the nervous system in the stimulation of erythropoiesis under prolonged or repeated hypoxia is disputed by many authors (Grant, 1950; Ardashnikova, 1952; Barbashova, 1960). There are grounds, however, for doubting certain of the ideas that have developed on the regulatory mechanisms of the blood system in oxygen starvation (Beller, 1957).

In collaboration with Yu.V.Nikolayenkov, we studied the reaction of the blood system to acute and repeated hypoxia in dogs (barometric pressure drop to 267 mm Hg for 2 hrs on each of six successive days). Under these conditions the short-term redistributive reaction of the blood system is distinctly manifested (erythrocytosis, reticulocytosis without change in blood composition, increase in the volume of circulating blood accompanied by a rise in its absolute erythrocyte count). The repeated effect of hypoxia induces an increase in /64
the "background" of the red blood indices. These changes are due to an intensification of erythropoiesis, as indicated by the leftward shift in the reticulocytal formula, the characteristic changes in the acid erythrograms, and the results of a study of punctates of the bone marrow and the rate of incorporation of radio-iron in the newly formed erythrocytes.

In experiments on dogs with bilateral denervation of the carotid sinuses, the participation of these zones in the regulation of the respiratory surface of the blood, under condition of oxygen insufficiency, was determined as follows: The reflex mechanism that originates in the chemoreceptors of the sinocarotid zone is not the only one involved in the development of acute hypoxic erythrocytosis. The significance of this mechanism apparently consists in its ensurance of a rapid appearance and cessation of the erythrocytal reaction (on elimination of the chemoreceptors of the carotid sinuses, this reaction loses its "synchronism" with the time of action of acute hypoxia). The participation of this reflex mechanism in the stimulation of erythropoiesis seems more important. In our experiments, the elimination of the sinocarotid zones made the animals unable to give an erythropoietic reaction to the repeated action of hy-

poxia. These results do not, however, exclude the possibility of the stimulation of erythropoiesis, even without the sinocarotid chemoreceptors in fulminant or prolonged hypoxia.

Experiments after splenectomy confirmed the importance of the spleen for the acute hypoxic reaction of the blood system. It is interesting that splenectomized dogs should have lost not only the power of erythrocytal reaction but /65 also of reticulocytal reaction to short-term effects of oxygen insufficiency. In these animals we also noted the absence of an increase in the "background" of the hematopneic index. Similar results were obtained on two dogs with the spleen transplanted to the neck (in one case the autotransplanted organ was reinnervated through the cervical branch of the vagus). On the basis of these experiments it must be recognized that, in oxygen starvation, the spleen participates not only in the mechanism of redistributive erythrocytosis but also in the stimulation of erythropoiesis.

In experiments on puppies of various age we found that neither the redistributive nor the erythropoietic reaction of the blood system to hypoxia are pronounced at birth, but are formed regularly during postnatal ontogenesis. This may be connected with the fact that the mechanisms governing these reactions are likewise not formed at birth. For example, we found that the function of the spleen as an organ of the blood system at various stages of individual development of the organism is distinguished by pronounced peculiarity. This peculiarity is largely responsible for the age-group features of the reaction of the blood system to acute or repeated oxygen starvation.

ON THE RELATIONS BETWEEN HEMODYNAMICS, REGIONAL CIRCULATION AND OXYGEN EXCHANGE IN THE TISSUES

/66

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The problem of the study of the mechanisms participating in the complex adaptive reactions of the organism and its various organs and tissues to the continuously changing conditions of the environment is one of the most topical in modern physiology.

The changes in the parameters of the environment, over the intermediary of various elements of the complex neurohumoral regulation, modify the functional state of the organism and its systems, maintaining for it, within certain limits, a constant internal medium.

The hemodynamic shifts and changes in local circulation are of great importance in the adaptive and compensatory reactions.

As a result of the work of many investigators, various aspects of the activity of the cardiovascular system have been studied in great detail. New confirmations have been found for Pavlov's proposition that the cardiovascular system is self-regulated. The studies by USSR investigators on the organization of the regulatory apparatus of the circulatory system have won wide recognition. Nevertheless, present knowledge on the laws of the functioning of the circulatory system as a whole is still insufficient. A comparison of a large number of indices, characterizing various aspects of the activity of the cardiovascular system and defining the interrelations involved, may help to conceive a fuller picture on the activity of the circulatory system. /67

The minute volume and the systemic arterial pressure, which characterize the functional state of the circulatory system as a whole, do not reflect the features of the local circulation of various organs and tissues. Still, changes in the local blood flow affect the magnitude of these indices just as the general hemodynamic shifts affect the state of the peripheral circulation.

The study of the relation between general hemodynamics and local blood circulation under normal conditions and on models of various states of the organism is of interest for defining the laws of regulation of the circulation, the characteristics of hemodynamics and of blood flow through the organs, and for understanding the relations between the vascular reactions in various regions of the body.

For a number of years, the Laboratory of Circulatory Physiology, Institute of Physiology imeni A.A.Bogomol'ts, UkrSSR Academy of Sciences, has conducted comparative studies on the changes in hemodynamics and local circulation, under exclusion of the pressoreceptor apparatus of the carotid sinuses, in acute aortic occlusion, after injection of catecholamines, in hypothermia, hypoxia

and experimental hypertension (M.I.Gurevich, A.I.Vyshatina, A.G.Kartseva, M.A. Kondratovich, M.M.Povzhitkov, S.A.Bershteyn, T.Mansurov, V.A.Tsirul'nikov, and others).

Certain features of the interrelations of general hemodynamics and local blood flow have been studied in a number of organs and under various conditions.

The study of the interrelations of hemodynamics, tissue circulation, and /68 oxygen exchange in the tissues is an important problem of circulatory physiology. The close relation between these indices has recently been demonstrated by several authors.

On decrease in the O_2 tension in the surrounding medium, disturbance of the "oxygen transport" function of the blood, decrease in blood flow, or increase in oxygen consumption of the tissues, hemodynamic shifts develop directly toward compensation of the general and local disturbances of oxygen exchange.

A pronounced hypoxia induces not only changes in respiration but also distinct hemodynamic shifts (changes in cardiac output, systemic arterial pressure, total peripheral resistance, circulation volume, etc.). With respect to the variations of the minute volume, in the various forms of hypoxia, the changes in partial oxygen pressure in the tissues and venous blood are apparently of extreme significance (L.L.Shik, 1964).

Contradictory results as to the changes in systemic arterial pressure in hypoxia have been reported (N.N.Sirotinin, 1939; I.V.Bazilevich and I.M.Turovets, 1938; P.I.Yegorov, 1937, 1941; Gorlin and L'yuis, 1954; Braun, 1958; N.V. Lauer, A.Z.Kolchinskaya and V.V.Turanov, 1960; S.A.Bershteyn, 1965).

It has been proved that hypoxia is accompanied by considerable changes, of varying intensity, in the blood flow in various organs (M.Ya.Marshak et al., 1948; Hayton et al., 1962, 1964, and others).

The changes in local blood flow during hypoxia are complex and are due /69 to interrelations of the central and local influence of oxygen insufficiency on vascular tonus and hemodynamics.

The question of the mechanisms of self-regulation of the tissue circulation is of great interest, although still quite controversial. Apparently, not one of the hypotheses attempting to explain this mechanism is able to give an exhaustive and universal explanation. Changes in the pO_2 of the blood and tissues may be important in the regulation of tissue circulation. In considering the numerous hypotheses on the mechanism of self-regulation of blood flow to the organs, it must be remembered that, in the intact organism, the regulatory changes of local blood flow should not lead to an overloading of the heart or to a sharp change in the systemic arterial pressure. Here, a complete and thorough understanding of the mechanism, by which the optimum relations between tissue consumption of nutrients and hemodynamics and local blood supply are achieved, is one of the most important problems of circulatory physiology.

OXYGEN WANT OF THE ORGANISM AND PHOSPHOLIPIDE METABOLISM IN THE BRAIN

/70

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It has previously been shown that oxygen want of the organism, caused by a decrease in atmospheric pressure, leads to a lowering of the metabolic rate of total phospholipides in the brain. The synthesis of phospholipides in rat brain tissue decreased by 30 - 50%, depending on the degree of hypoxia.

In this work, we studied the level of the individual phospholipide fractions and the metabolic rates of their phosphate groups in the cerebral cortex of rats, under oxygen insufficiency induced by a two-day exposure of the animals in the altitude chamber to reduced atmospheric pressure.

The animals were subjected to two different degrees of anoxemia: 1) First group - atmospheric pressure of 240 mm Hg; 2) Second group - atmospheric pressure below 180 mm Hg. The level of the individual phospholipide fractions in the brain was estimated from the lipidic phosphorus content, in γgm per gram of wet tissue. The metabolic rates of the phosphate groups of the individual fractions were estimated from the rate of incorporation of radioactive phosphate in each fraction and were expressed as the percentage ratio of the specific radioactivity of the fraction to the total specific radioactivity of the inorganic phosphate of the brain tissue.

It was shown that two hours in the altitude chamber, for both groups, induces no basic change in the content of all the phospholipide fractions studied in the brain tissue of the rat, even in the most advanced stage of hypoxia. /71 Oxygen starvation induced a distinct, statistically significant, lowering of the rate of renewal of the phosphate group in all fractions, but the extent of this decrease differed for the different fractions. In rats of Group 1, the rate of renewal of the fractions of aminophosphatides and lecithins was decreased most, and that of the fractions of the phosphatide acids and polyglycerophosphatides, phosphoinositides, and sphingomyelins was decreased least. The difference in the degree of decline of the metabolic rate with respect to these two groups of phospholipides is statistically significant. The greater degree of oxygen want (rats of Group 2) does not result in a further decrease in the rate of exchange of the fractions of phosphatidic acid and polyglycerophosphatides, aminophosphatides, and sphingomyelins, whereas the fractions of phosphoinositides and lecithins react to increasing hypoxia by further lowering of their metabolism.

These data permit the conclusion that the individual phospholipide fractions of the brain tissue of rats have different degrees of sensitivity to oxygen starvation of the organism. This differential sensitivity has to do with the chemical structure and biosynthesis pathways of the phospholipide fractions, and with their role in maintaining the activity of the central nervous system.

SOME DATA ON THE REACTION OF THE EXTERNAL RESPIRATION AND MYOCARDIUM TO A DECREASE IN THE OXYGENATION OF THE ARTERIAL BLOOD IN HEALTHY PERSONS

/72

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The reaction of the system of external respiration and myocardium to decreased oxygenation of the arterial blood in healthy subjects has not been sufficiertly studied, and the literature data are scanty and inconsistent.

To study this problem, we examined 102 young athletes, mostly males, highly qualified ard of long experience in different fields of sports, and 17 healthy non-athletes.

Oxygeratior of the arterial blood was decreased by three methods: rebreathing (using a Type 35 Hungarian spirometabolograph), inhalation of a mixture with 10.3 - 10.5% ard 14 - 15% of oxyger (using an SG-I spirograph). Each time, a lime carbor dioxide absorber (CCA) was used, so that the percentage of CO_2 under the bell at the end of each experiment did not exceed 0.2 - 0.3%. In addition, the oxyger level of the arterial blood was determined by an O-36M oxyhemograph; the oxygen level was not allowed to fall below 65 - 70% since, according to the literature (Altukhov, Balakhovskiy, Malkin, 1954), a drop below this level may lead to considerable changes in the central nervous system.

The studies covered: reaction of external respiration [absorption of oxygen per minute, depth and frequency of respiration, minute volume (MV), oxygen utilization factor (OU)], electrocardiogram, and vectorcardiogram.

In all three methods, the onset of the decline in oxygenation and the /73
time of reaching 65 - 70% oxygen level varied among the subjects and fluctuated from 0 to 5 min (in most subjects, in the 2nd min) and from 5 to 10 min and longer (in most subjects, in the 6th min). The earlier the decline in oxygenation commenced, the more rapidly was the maximum reached.

Thus, it is obvious that the degree of decline in the oxygenation of the arterial blood does not depend on the time of exposure alone, but also on the individual traits of the subject (rate of oxidative processes, degree of utilization of compensatory mechanisms, etc). This is of particular significance for the rebreathing method. Obviously, the estimate of the reaction to arterial hypoxemia must not be based exclusively on the time of exposure but requires some oxyhemometric control.

The reaction of the main functional indices of external respiration (minute volume, oxygen uptake per minute, and oxygen utilization factor) to an increase in arterial hypoxemia is also highly individual. A total of 14 different combinations of changes in these indices were found, including complete absence of any change in external respiration.

We divided these combinations into three groups, based on the change in the oxygen utilization factor which we considered the factor best characterizing the effectiveness of aeration.

As "rational reaction" of the external respiration system we defined the increase or constancy of the OU, regardless of the type of changes in MV and oxygen absorption (8 combinations). Any decrease in OU was considered an "irrational reaction" of the external respiration to arterial hypoxemia (5 combinations). The third group was characterized by constancy in OU, in MV, and in /74 oxygen uptake.

TABLE 1

CHARACTER OF REACTION OF EXTERNAL RESPIRATORY SYSTEM IN VARIOUS METHODS OF INDUCING ARTERIAL HYPOXEMIA IN ATHLETES

Percent Oxygen Saturation, Arterial Blood	Rebreathing Method (64 Subjects)			Inhalation of a Mixture with 10% O_2 (24 Subjects)		
	Rational	No Reaction	Irrational	Rational	No Reaction	Irrational
	%		%	%		%
90%	24 37.5	4	36 56.2	2 8.3	4	18 75.0
70-65%	13 20.3	-	51 79.7	9 37.5	1	14 58.3

In athletes during rebreathing tests, the number of rational reactions decreased with increasing arterial hypoxemia, while the number of irrational reactions increased. At 65 - 70% oxygen saturation of the blood, there were no cases of failure to react (Table 1). The opposite picture was noted on inhalation of a gas mixture with 10% oxygen: here, the number of rational reactions at the same degree of arterial hypoxemia (65 - 70%) increased.

The reaction rate showed a decrease by 17% in the rational reactions of the external respiratory system in rebreathing tests with increasing hypoxemia, and an increase by 29% on inhalation of 10% oxygen. The opposite relation holds for the irrational reactions (a 23.5% increase and a 17% decrease, respectively).

The correlation coefficient in rebreathing is 0.447; in inhalation of 10% oxygen it is negative and is equal to -0.705. Consequently, athletes have the opposite degree of parallelism between the groups of reactions of the ex- /75 ternal respiratory system, depending on the method by which arterial hypoxemia was induced.

Evidently, when a gas mixture with a constant low oxygen content (10%) is breathed for several minutes, the function of external respiration has time to adapt to the low oxygen content of the inhaled mixture. This is a sign for the good functional state of the athlete's body.

The above statement is confirmed by our analysis of the data from successive inhalation of 10 and 15 - 14% of oxygen per minute.

On inhalation of a gas mixture with 14 - 15% oxygen, the indices vary during the first or second minute. All functional indices of external respiration will then stabilize despite the gradual decline of the arterial blood oxygen level to 14% at the end of the experiment.

This pattern is even more distinct in athletes inhaling a 10% oxygen mixture. By the end of the first minute, the MV increases to 14%, while the oxygen consumption and the OU decrease 20 and 27%, respectively. Beginning with the second minute, these functional indices become established at a new level and are stabilized, with fluctuations of ±5%, until the end of the experiment, i.e., the MV rises to 30% above the initial value within 10 min, the OU declines by 20%, and the oxygen consumption remains within the original range. Bearing in mind that the percentage of carbon dioxide in the system of the apparatus does not exceed 0.2 - 0.3% (according to Kholshchen) at the end of the experiment, the degree of arterial hypoxemia may be considered the dominant influence on the function of external respiration.

As for rebreathing, in which the oxygen content of the inhaled mixture progressively decreases from the first minutes, the organism is apparently unable to adapt itself. This is confirmed by the decrease in number of rational re- /76
actions of the external respiratory system to an increase in the degree of hypoxemia. Thus, during the first two minutes of the experiment it was 56.2%; in the 3rd - 4th minute, 35.9%; in the 5th - 6th minute, only 25.6%.

An analysis of the reactions of the external respiratory function in athletes to arterial hypoxemia in rebreathing divided by minutes, showed that the oxygen consumption during the entire test remained equal to the original value, with minor fluctuations. The MV begins to increase and reaches an average of 12% above its initial value by the fourth minute, when the oxygen content of the inspired air has dropped to 14% and the oxygenation of the blood has decreased to 85 - 87%. Beginning with the fifth minute, there is a sharp increase in the MV (by 87%), a decrease in the OU (by 53%), and a decrease in the oxygen saturation of the arterial blood (to 65%).

In rebreathing, the reaction of the functional indices of external respiration in healthy non-athletes does not differ qualitatively from that of athletes. There is only a quantitative difference: When the oxygen content of the inspired air drops to 14%, the MV increases by 10% over the initial level; this begins at the sixth minute and is accompanied by an 11% decrease in oxygen consumption, by a drop in blood oxygenation to 80%, and by a corresponding decline in the OU. It is interesting to note that, in athletes, after a decline in blood oxygenation to 80%, the MV will show an average increase of 30%.

This reaction in non-athletes to a decrease in oxygenation of the blood indicates an incomplete correlation between respiratory and circulatory functions. The importance of completeness of these correlations is confirmed by a comparison of the reaction of the external respiratory system in athletes in various /77
functional states, i.e., at various degrees of training.

Well-trained athletes, at the beginning of the experiment, i.e. when the decline in oxygen saturation of the arterial blood was still small, exhibited rational and irrational reactions of the respiration in the same number of cases. As the oxygen saturation decreases, the number of irrational reactions increases. Among those with moderate training, and especially those with inadequate training, the number of individuals with poor respiratory reaction is greater, even at the beginning of the test.

TABLE 2

INTENSITY OF CHARACTER OF ECG CHANGES IN ATHLETES IN VARIOUS METHODS OF INDUCING ARTERIAL HYPOXEMIA

Method	ECG Findings		
	Favorable	Adaptive	Unfavorable
Rebreathing	56.9	15.5	27.6
Inhalation of 10% CO_2	66.7	23.8	9.5
Inhalation of 15-14% O_2	85.7	7.1	7.1

As for the changes in the myocardium, a low oxygen content of the inspired air on rebreathing (sometimes reaching 5%) may explain the high percentage of unfavorable ECG findings (Table 2). Favorable ECG reactions, in this Table, mean slight or no flattening of the T wave; adaptive reactions mean considerable flattening of the T wave; unfavorable reactions mean two-phase negative T waves or the paradoxal reaction.

A comparison of the character of the reaction of the external respiratory /78 system to arterial hypoxemia down to 65 - 70% with the changes in the myocardium showed complete absence of correlation between them.

In the groups with different respiratory reactions, the number of persons with myocardial changes was the same. In other words, even a good respiratory reaction may still be accompanied by deleterious myocardial changes, and conversely, an unfavorable respiratory reaction may be unaccompanied by myocardial changes.

It seemed important to learn whether the myocardial changes depend on the functional state of the organism, i.e., on the degree of training. The percentage of increase in heart rate over its initial value in well-trained athletes was found to be lower than in those with inadequate training (Table 3).

This is particularly distinct when oxygenation declines to 90%. On a drop to 65 - 70%, this difference is smaller but still persists. Recovery of the /79 heart rate at the third minute after completion of the experiment was likewise encountered more often in the trained subjects. This was less marked in the increase of the Q - T interval by more than 0.04. The myocardial changes were un-

favorable in athletes with varying degrees of training, with a strictly similar percentage of cases (27% in each group.

TABLE 3

CHANGES IN HEART RATE (HR) AND IN THE Q - T INTERVAL WITH DEGREE OF TRAINING

Degree of Training	Increase in HR, %		Recovery of HR in 3 min, %	Q - T 0.04, %
	at 90%	at 70-65%		
Good	10.7	34.3	64	56
Moderate	13.7	31.0	45	63
Inadequate	19.2	41.5	41	63

Thus while the changes in the heart rate and the external respiratory functions showed a dependence on the degree of training, myocardial changes due to arterial hypoxemia were independent of the training state of athletes, i.e., of the functional state of the organism.

This fact, as well as the complete absence of any correlation between the changes in the external respiratory function and those of the myocardium, permit us to postulate that in athletes with a high-level functional state, the deleterious myocardial changes in arterial hypoxemia reflect not so much the functional state of the cardiac muscle as they reveal latent morphological alterations.

These morphological alterations, owing to the high functional level of the organism, are not disclosed in conventional function tests and have no effect on the degree of training.

This is favored by high development of functional coordination in athletes, creating the conditions for full mutual compensation, by the individual organs and systems, of various morphological alterations which, in routine examination, may excape detection.

Thus, our data permit the following conclusions:

1. The effect of arterial hypoxemia on the organism can be studied only /80 if allowance is made for the changes in oxygen saturation, since the degree of arterial hypoxemia cannot be determined from the period of time during which the subject has been rebreathing or inhaling a hypoxic mixture.

2. The rebreathing test and the hypoxic mixture inhalation test are not identical and have different effects on the body.

3. The main factor inducing changes in aeration and in the myocardium, with

various methods of inducing arterial hypoxemia, is the extent of the decline in oxygen saturation of the blood.

4. The myocardial changes during arterial hypoxemia do not depend on the degree of training.

REACTIONS OF VENOUS DEPARTMENTS OF CERTAIN VASCULAR REGIONS IN MYOCARDIAL HYPOXIA

/81

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Several authors have recently reported regular changes in local blood circulation during experimental myocardial hypoxia (Turevich, M.I.; Dokukin, A.V.; Povzhitkov, M.M.). In particular, it was found that the vascular resistance of the limbs increases whereas that of the mesenterial blood vessels decreases. These effects may be due either to corresponding changes in arterial tonus or to shifts of the hemodynamics in the venous system, for example, by obstruction of the blood flow as a result of cardiac insufficiency, or its facilitation in the case of venous dilatation or concentration of blood in other vascular regions. With the object of defining the role of the various sectors of the local blood circulation in these effects, we investigated the volume changes of the blood vessels in the limbs and intestines, and the changes in the lesser circulation with the left heart in acute myocardial hypoxia. The volume characterizes the state of the venous sector of the blood stream.

The experiments were performed on cats. To induce cardiac ischemia, the descending branch of the left coronary artery was temporarily compressed at the base. The volume of blood flowing through the limbs and intestines was recorded by a photoelectric drop counter, with its transmitter placed along the iliac or mesenteric vein. The cardiac output was measured by a flowmeter in /82 the ascending aorta. The radioactive tracer method was used to determine the time of flow of the blood through the various sections: abdominal aorta - iliac vein; thoracic aorta - mesenteric vein; pulmonary artery - ascending aorta. The volume was calculated by the Stewart-Hamilton principle, multiplying the blood flow in mℓ/sec by the time of flow in sec/cm (cf. Meyer and Zirler, and others).

It was established in the experiments that the volume of the vascular flow in the limbs, which was 7.55 mℓ on the average, decreases after compression of the artery to 6.1 mℓ and that of the intestinal flow, from 9.4 to 8.5 mℓ. The volume of the lesser circulation from the left heart increases on the average from 16.8 to 20.5 mℓ. Vagotomy at the height of the neck considerably weakened the influx of blood into the pulmonary stream, but had no effect on the changes in volume of the peripheral vascular regions.

The experimental results permit certain conclusions: The decrease in volume of the blood stream in the limbs suggests the absence of major obstacles to the efflux of blood. Thus, the increase in resistance of this vascular region must be due to the compensatory increase in arterial tonus. As established previously, the venous pressure increases somewhat under myocardial hypoxia. The decrease in volume of the blood vessels in the intestines and limbs, in this case, may be explained by an acute constriction of the veins. It should then be assumed that the decrease in the resistance of the mesenteric stream is not

due to a dilatation of the veins with the resultant greater efflux but to arterial hypotonus. This conclusion is also confirmed by the fact that, after /83
vagotomy, the intestinal vascular resistance no longer decreases in response to myocardial ischemia but increases instead, while the reaction of the venous stream remains unchanged. The influx of blood in myocardial hypoxia takes place in the left heart and in the lungs. This phenomenon is simplest explained by insufficiency of the left ventricle. The role of vasomotor influences still requires further study. These data demonstrate the great differentiation of the reactions of the vascular system to exogenous influences. A distinctly specific character is observed not only in the behavior of the individual vascular regions, but also of various sectors of the same stream.

THE EFFECT OF OXYGEN ON CERTAIN FUNCTIONS OF THE ORGANISM /84

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Interest in studies on the effect of high partial oxygen pressure on the organism has greatly increased in recent times. The widespread use of oxygen in clinical practice, aviation and space flights, diving, etc., confronts physiologists with the task of defining the upper limits of partial oxygen pressures still safe for the human organism.

The various authors are not in agreement on the permissible limits of oxygen use at normal and elevated pressures, and the adaptive capability of the organism to oxygen is unknown. Many authors believe that the safe upper limit of prolonged oxygen inhalation for human subjects is a partial pressure of 425 mm Hg (about 56% of oxygen at atmospheric pressure). However, experimental data in support of this view are insufficient. A higher partial oxygen pressure has a toxic effect so that respiration in such a medium had to be limited to short periods, of a duration inversely proportional to the partial oxygen pressure and varying within relatively wide limits.

The author and his coworkers investigated a number of physiological functions of the organism in an oxygen-rich atmosphere under normal and elevated pressure.

Of special interest, among the various effects, is the finding that mice, after a prolonged stay (10 days) in a high-oxygen medium (60%) according to /85
I.S.Breslav's method, spontaneously searched out an oxygen-rich gas medium. The observed changes in certain functions of the central nervous system and in the gas exchange on prolonged inhalation of this gas mixture (up to 40 days) are also of a certain interest.

Our experimental material indicates the adaptive capability of the organism to high partial oxygen pressures, on the basis of the adaptive reaction developed in hypoxemia; however, the reaction here is in the opposite direction, i.e., a restriction in oxygen supply to the tissues and organs rather than an increase. The respiratory and circulatory systems play a major role in this adaptation. The degree of pulmonary aeration and the rate of blood flow decrease, the heart rate slows, the blood vessels contract (especially in the brain), there is deposition of blood, reduction in respiratory metabolism, and other reactions.

A typical example of such reactions is one of our experiments on human subjects and dogs, inhaling oxygen under a pressure of 2 - 3 atm. abs. (kg/cm^2 abs). Human subjects, subjected to this pressure, exhibited spasm of the capillaries of the nail matrix, decrease in cutaneous temperature, and drop in total respiratory metabolism. In determining the respiratory metabolism, we found transient increase in oxygen uptake, connected with the excessive physical dis-

solution of oxygen in the liquid media of the organism. An indirect proof of the restricted supply of oxygen to the tissues is also provided by our determinations of the oxygen saturation of the saliva collected from the parotid duct of dogs that had been subjected to an oxygen pressure of 2 and 3 atm. abs. It was found that, in most of the experiments at 3 atm. abs., the oxygen saturation of the saliva was lower than at 2 atm. abs. This fact is apparently connected with the marked vasoconstriction and the slowing of the blood flow in the experiments at 3 atm. abs. /86

Subsequent studies showed that, under oxygen pressures exceeding 3 atm. abs. or at increasing oxygen exposure time, the physiological reactions become pathological and are now directed toward increasing the oxygen supply to the tissues: higher pulse rate, increased pulmonary aeration, etc.

Our experimental material and the literature data indicate that the safe period for oxygen inhalation lies within the time limits of the physiological adaptive reactions of the given organism.

REACTIONS OF THE HUMAN CARDIOVASCULAR SYSTEM TO HYPEROXIA* /87

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1. The reaction of the human cardiovascular system to hyperoxia has usually been studied under oxygen pressures not exceeding 3 atm. abs. and mostly only in the initial phase of its effect (Benke et al.; A.G.Zhironkin; P.A.Sorokin; and others).

In our work we used higher oxygen pressures for this purpose (3.5 and 4.0 atm. abs.) and compared the effect with the known results of low oxygen pressures of 1.3 atm. abs. We also increased the time of exposure of the subjects to oxygen under pressure, until appearance of the first symptoms of oxygen intoxication.

2. The test subjects were professional divers, who were made to inhale oxygen in a sealed device, placed in a special chamber. The pressure in the chamber was produced by compressed air. Each subject, first under ordinary conditions and then while inhaling oxygen under pressure, was subjected to the following tests: arterial blood pressure (on a sphygmooscillograph), ECG in /88 the three standard leads, plethysmogram from the finger, and respiration (on a pneumophotoelectroplethysmograph). We also determined the field of peripheral vision on a portable perimeter.

We also calculated other factors, including stroke volume (according to Starr), minute volume, and peripheral resistance (according to Savitskiy).

3. Under the action of oxygen at 1.3 atm. abs. pressure, a one-phase reaction of the cardiovascular system was observed in all subjects. The pulse slowed (8 - 20 per min), the minute volume decreased (1.5 - 2.63 ltr), while the diastolic pressure increased (by 9 - 22 mm Hg), and the peripheral resistance increased (by 510 - 2150 dynes/cm^2/sec). These shifts remained constant during the entire time of oxygen inhalation under pressure (up to 3 hrs). Such changes in the cardiovascular system may be regarded as an adaptive reaction of the organism directed toward decreasing the transfer of excess dissolved oxygen to the tissues.

4. Under the action of oxygen at 3.5 atm. abs. pressure, the adaptive reaction of the cardiovascular system (decrease in pulse rate by 12 - 28 beats/min, decrease in minute volume by 1.72 - 2.65 ltr, increase in peripheral resistance

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* Presented at the Fifth Scientific Conference, in Memory of Academician L.A. Orbeli.

by 580 - 2320 dynes/cm^2/sec etc.) lasted from 1 hr 20 min to 2 hr 18 min. This was followed by a change in pulse in the opposite direction (2 - 7 beats per /89 minute faster) and in minute volume (increase of 0.28 - 0.65 ltr). The field of peripheral vision showed concentric narrowing. This was accompanied by the first symptoms of oxygen intoxication (nausea, headache, dark spots before the eyes, etc.).

This meant that the adaptive phase of the reaction of the cardiovascular system had given way to the toxic phase.

5. Under the effect of higher oxygen pressures (4.0 atm. abs.), we also observed a two-phase reaction of the cardiovascular system, with similar changes of the parameters. The difference was that, in some of the subjects who were most predisposed to oxygen intoxication, the first adaptive phase of the reaction was brief (13 - 23 min) followed immediately by the first symptoms of oxygen poisoning.

6. The results, compared with the literature data, permit conclusions as to the general character of reaction of the human cardiovascular system, its phasic course, and the differences in its manifestations under the action of different oxygen pressures.

PHYSIOLOGICAL MECHANISMS OF THE CHANGES IN RESPIRATORY METABOLISM AND BODY TEMPERATURE DURING HYPOXIA

/90

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1. Oxygen is a necessary element of life, and a decrease in its content in the medium ultimately leads to depression of metabolism and death. Lowering of the respiratory metabolism and a drop in body temperature, however, already occur at relatively moderate hypoxia.

2. Two hypotheses can be advanced to explain this phenomenon. First, even a relatively small decrease in the partial oxygen pressure in the medium decreases its tension in the tissue cells to below the "critical" value. This leads to a decrease in the rate of oxidation of the respiratory enzymes and involves a lowering of the respiratory metabolism because of the insufficiency of oxygen in the tissues. Second, hypoxia acts primarily on the physiological regulatory mechanisms of respiratory metabolism and heat production of the entire organism.

3. Details on the first hypothesis include: The characteristic physical properties of oxygen (Szent-Gyorgi, 1960), its very low "critical" tension in the tissues relative to the rate of oxidation of cytochrome oxidase (Wentzler, 1941; Elliot and Henry, 1946; Bender and Kise, 1955; Bronck, 1960; Shertlin, 1961; and others), the available calculations on tissue oxygen tension (Optitz and Schneider, 1950; Tovs, 1960; and others), a direct determination of the respiratory metabolism of the brain (Hirsch et al., 1955; 1961), and certain other data are used as basis for the hypothesis that, in moderate hypoxia, the lowering of the respiratory metabolism of the entire organism is independent of /91
the direct oxygen insufficiency in the tissues.

4. Details on the second hypothesis comprise: Experimental results are given to prove the depressive influence of hypoxia on the specific thermoregulatory forms of muscular activity; chills and "thermoregulatory tonus". In various animals, a distinct correlation was noted between the extent of depression of these forms of muscular activity and the degree of lowering of the respiratory metabolism and body temperature in hypoxia. The physiological mechanisms of phenomena of this kind are discussed. Data are presented on the direct studies of the function of the heat-regulatory centers in the hypothalamus in hypoxia (V.A.Konstantinov). The assumption is made that, at a relatively low temperature of the medium, the primary cause of the lowering of the respiratory metabolism and the decrease in heat production of the organism is the depression in chemical heat regulation.

5. The changes in physical heat regulation in hypoxia are considered.

6. On the basis of literature data and experimental data obtained in the

author's laboratory, a general scheme is presented for the disorders of respiratory metabolism and heat exchange of the organism in hypoxia.

EXPERIMENTAL DATA ON THE OXYGEN REGIME OF CERTAIN ORGANS IN TRAUMATIC SHOCK

/92

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The oxygen regime of individual organs occupies an important position in the oxygen balance of the body; organs such as the brain, heart, liver, kidneys, etc. range first in this respect.

In studying the oxygen balance of the organism in traumatic shock, we investigated the local circulation, the utilization of oxygen by the brain, liver, and kidneys, the oxygen tension in these organs, and the oxygen tension of the heart. The results were compared with the general hemodynamic changes and with the respiration. The local circulation was judged from the flow in the afferent or efferent blood vessels. The utilization of oxygen was determined from the arteriovenous oxygen difference, calculation of the oxygen utilization factor, or direct calculation of the oxygen uptake of the organ. The oxygen pressure was measured polarographically, using both the classical method, with platinum and silver chloride electrodes, and the Epstein system without batteries.

We found that hypoxia of the circulatory type occurs in traumatic shock. The degree of hypoxia of the various organs is not uniform and is determined by the features of local circulation. First of all, as the shock progresses, the oxygen regime of the kidneys is disturbed, followed by the liver, brain, and /93 heart.

Thus, the blood flow through the kidneys decreases in the torpid phase of shock to less than a tenth of normal while the oxygen utilization factor increases, and the renal oxygen utilization is badly disturbed.

The blood flow through the liver decreases in the torpid phase by a factor of 1.5 while the oxygen utilization factor increases; despite this, the oxygen tension in the liver decreases 2 - 3 times below its normal value.

The oxygen tension in the cerebral cortex decreases markedly only in the terminal phase of shock, although a reduction in circulation appears considerably before that. The oxygen utilization factor of the brain increases with increasing degree of shock.

The oxygen pressure in the heart was on the whole highest of all the organs mentioned, and fluctuated parallel to the systemic arterial pressure, i.e., rising in the erectile phase of shock, stabilizing during its torpid phase, and decreasing as shock deepened.

ADAPTATION OF THE ATHLETE'S HEART TO WORK DURING HYPOXIA /94

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The adaptation of the athlete's heart to muscular stress under conditions of oxygen starvation was studied: 1) during repeated work on the bicycle ergometer while inhaling a low-oxygen gas mixture (15% oxygen, 85% nitrogen); 2) after a 100-m dash with voluntary retention of breath.

During repeated work on the bicycle ergometer and during the recovery period, the ECG (according to Nebb) was taken synchronously with the phonocardiogram, and the arterial pressure was measured. After the dash, the ECG was taken in the three standard leads and the arterial pressure was studied. The subjects were 63 athletes. In all, 77 studies were made in the gas-mixture experiments, and 19 at the athletic field after the event with breath-retention dash. Work with normal respiration was used as the control of the functional state of the heart during athletic workout.

Under the conditions of work during respiration of a gas mixture with 15% oxygen, the blood oxygen saturation in most of the athletes (66%) fell to 49 - 70%. It is well known that a decline in this saturation to 70 - 40% is accompanied by symptoms of decompensation of the body functions (stage III of hypoxia according to A.Z.Kolchinskaya, 1963). During such hypoxemia the athletes performed work of a total power of 9000 kg-m or more.

During the work under conditions of hypoxia, the heart rate increased /95 continuously and reached 0.42 - 0.35 sec at the end of the third minute. Similar work, while breathing normal air, was accompanied by a slight decrease in oxygenation (to 94 - 90%) and a somewhat slower heart beat (RR 0.56 - 0.40 sec). During the first 15 sec of work, the heart rate (as well as the systolic pressure) were almost the same, both with the gas mixture and with normal air. Apparently, the conditioned-reflex mechanism, connected with muscular activity is of prime importance in the initial increase in heart rate. In a number of subjects (13%), there was a distinct impairment of the rhythm by the end of the work during the second and third repetition: an extrasystolic rhythm, and more often a ventricular one. In normal air, no extrasystoles were recorded at all. After the end of the work under hypoxic conditions, the heart rate slowed distinctly; in many of the subjects, during the second minute of recovery, an arrhythmia of the nature of a sinoauricular block was noted.

The PQ and QT intervals shortened during the work (PQ to 0.10 - 0.09 sec, QT to 0.23 - 0.20 sec). Work under hypoxia was accompanied in six subjects by a lengthening of the PQ interval to 0.21 - 0.23 sec. As a rule, the P and R waves were moderately higher (P up to 1.5 - 2 mm, R up to 11 - 12 mm).

During the first minute of work under hypoxia, a considerable flattening of

the T wave was noted, almost reaching the iso-line and even going beyond it into the negative and 2-phase (15%), followed by a rise reaching the initial level by the end of the work and being, by the second minute of recovery, twice as high as the initial level or even higher. The blood-oxygen curve forms a /96
peculiar "scissors" with the curve of variation of the height of the T wave. During work in normal air, the change in the height of the T wave differed substantially. By the end of work under hypoxia, a number of subjects showed signs of impairment of the coronary blood supply, a decrease of the S-T interval to 1.5 - 2 mm.

Muscular work under hypoxia was accompanied by a pronounced rise in systolic pressure to 170 - 180 mm, and in some subjects to 200 - 210 mm; with normal air breathing, the rise in systolic pressure was about the same, or 10 - 15 mm less.

Work under hypoxia was accompanied by a marked contraction of the mechanical systole to 0.19 - 0.17 sec. Very often the second heart sound appeared about 0.05 - 0.09 sec before the end of the T wave (Hegglin syndrome). Evidently, the repetition of this syndrome in healthy subjects cannot be explained by an "energetic-dynamic" cardiac insufficiency. Presumably, it is not due to weakening of the ventricles but to an increase in the stroke volume of the heart or to hemodynamic disturbances.

The work "to exhaustion" at the end of the muscular activity (lasting 40 - 120 sec) permitted an additional determination of the reserve powers of the athletic heart to work under hypoxia conditions.

After a 100-m dash, with breath retention (repeated 10 - 15 times) the heart beat was accelerated to 0.40 - 0.45 sec/beat but was no faster than after the same runs with normal respiration. As the runs were repeated, high and stable heart beat values and a rise in systolic pressure were noted in 50% of the subjects. However, the ECG taken immediately after the exertion with breath retention showed certain peculiarities, apparently due to the influence of /97
the hypoxic factor on the heart: moderate slowing of the precordial-ventricular conduction, sharp rise in the height of the P wave (to 4 mm) and flattening of the T wave; only in three subjects did we note an inversion of the S-T interval by 1.5 - 2 mm and a passage of the previously positive T_3 wave to the negative side.

Thus, the adaptation of the athletic heart to work under extensive hypoxemia was characterized by certain features of the processes of excitation and by changes in the biochemical processes in the myocardium. On the whole, in spite of the slowness in the development of adaptation noted in many subjects, we may speak of high compensatory and reserve powers of the athletic heart in its fight against hypoxia.

FEATURES OF THE OXYGEN REGIME IN VARIOUS MUSCLES IN VIVO, OF CERTAIN SPECIES OF RODENTS

/98

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Very few methodological variants of the study of oxidative processes in tissues in vivo are in existence. Judging from the literature, the electrochemical methods of gas analysis are very promising in this respect. We used the principle of electrochemical measurement of oxygen for a comparative estimate of the oxygen tension in various muscles of intact animals (white rats and golden hamsters), in both acute and chronic experiments.

A gold-iron electrode couple is used for measuring the oxygen tension in the muscles. The electrodes, made and calibrated in the Laboratory, giving concordant and reproducible values of the diffusion flow of oxygen, were inserted in various muscles. The current was recorded on the paper tape of a series BD micrograph. The features of the oxygen regime in various muscles (masseter, trapezius, as well as triceps muscle of the shoulder, biceps muscle of the femur) were studied during rest, at predetermined oxygen loads (oxygen test) and under the action of agents decreasing and increasing the rate of oxidative processes in the tissues.

The oxygen tension in the tissues is one of the indices of the intensity of the oxidative processes taking place there. The higher the metabolism in /99 the tissues, the lower - other conditions being equal - will be their oxygen tension and vice versa. From this point of view, the relative estimate of the oxygen tension in the various muscles gives an idea as to the intensity and topography of the metabolism in the muscular system. In our studies, we found a certain mosaic of oxygen regimes (oxygen tensions) in the various muscles. In the masseter and trapezius muscles we noted low values of the basic background of oxygen tension and lower values for the oxygen test. In the triceps muscle of the shoulder and the biceps muscle of the femur, on the other hand, the oxygen level and the reaction to the oxygen test were high. These differences are statistically reliable and were evidently connected with the higher utilization of oxygen (high level of respiratory metabolism) in the muscles of the head and neck and less rapid use of oxygen in the muscles of the limbs.

The topographic features of the oxygen regime, observed in vivo in the muscular system, are in agreement with the results of our in-vitro experiments performed in collaboration with Z.S.Aresheva, A.R.Makarova, and A.I.Shcheglova, by the Warburg method. The intensity of respiration of homogenates of the masseter and trapezius muscles in white rats and golden hamsters is 1.5 - 2 times as great as in the muscles of the femur and shoulder. Under these conditions, the features of the enzymatic respiratory systems already appear, and it is un-

necessary to consider the influence of hemodynamic factors which may occur under in-vivo conditions. Without denying the possibility of such changes, there is still no reason to assume that the peculiarities of the oxygen regime in various muscles of intact animals are determined primarily by the specifics of the circulation in them. A relative estimate of oxygen utilization in muscles with varying blood supply shows that the changes in pO_2 and the circulation do not necessarily proceed in the same direction. In the muscles of the neck, where the /100 circulation increases, i.e., where the inflow of oxygen from outside increases, the oxygen tension is lower than in muscles with less intense circulation. The latter contain more free oxygen, in spite of the smaller inflow.

The primary reason for the difference in the pO_2 level in these muscles evidently does not lie in the particularities of the circulation but in the character of the metabolism in the muscles. It can be assumed that the various muscle groups have different energy potentials. The definite mosaic of the metabolism that has been found apparently reflects the enzymatic basis of the tissue energy mechanisms, maintaining homeostasis in the organism.

THEORY OF OXYGEN DYNAMICS IN TISSUES OF THE LIVING ORGANISM

/101

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In this paper, the oxygen transportation pathway is represented as a continuously descending cascade of levels of partial oxygen pressures in the alveoli, the arterial, capillary, and venous blood, and in the tissues.

The fundamental propositions of the theory of gas diffusion in the liquid and solid media of the organism are given, including theoretical and experimental data on this subject available at the present time.

Concepts on the principal barriers in the path of oxygen from the atmosphere to the cells of the organism. The difference in partial oxygen pressure between the alveoli and the atmosphere is considered; present data on alveolar-arterial, capillary-tissue, and lympho-cellular oxygen gradients.

Present ideas on the spatial and geometric position of the capillaries in the surrounding tissues. Model of tissue capillary cylinder as one of the principal theoretical models used for the analysis of gas diffusion.

Principal forms of O_2 diffusion in the tissues. Radial and longitudinal diffusion and significance in arterial and venous hypoxia. Levels of oxygen tension at the edge of the tissue capillary cylinder and their importance in the development of tissue hypoxia.

Idea of the "critical" level of oxygen tension as the primary factor limiting the respiration of the enzymatic systems.

Modern hypotheses of tissue hypoxia and anoxia of the organism, from the viewpoint of diffusion theory.

Discussion of levels of oxygen tension in the tissues after inhalation /102
of low-oxygen, high-CO_2 gas mixtures.

Certain features of pO_2 dynamics in the tissues during hypoxic and circulatory hypoxia. Connection between basic functional disorders in the organism with the level of the mean-tissue and minimum oxygen tension.

Technique of polarographic determination of oxygen as the primary method of in vivo study of the continuous dynamics of oxygen in the tissues of the organism.

THE ROLE OF HEMODYNAMICS IN THE REGULATION OF THE OXYGEN REGIME /103

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During phylogenesis and ontogenesis, constant values of pO_2 and qO_2, which are the parameters of the oxygen regime of the organism, are established in the alveolar air and in the arterial and venous blood. The values of these parameters, which decrease as the oxygen passes from the alveolar air to the venous blood, form a stepwise descending series of height and steepness which, on the one hand, is determined by the rate of oxygen consumption in the tissues and by the oxygen content of the surrounding medium and, on the other hand, by the functional capability of the oxygen transport systems.

A study of oxygen metabolism, as a process taking place in a definite regime (N.V.Lauer and A.Z.Kolchinskaya), permits a quantitative estimate of the role of each of the components of the oxygen transport system in the adaptation of the organism to conditions of varying pO_2 in the surrounding medium and to the muscular load, or to other factors that modify the oxygen regime of the organism.

The integral index, characterizing the supply of oxygen, is the quantity of oxygen supplied by the circulating blood to the tissues in unit time (qO_2a). At constant arterial blood oxygen level, qO_2a is a function of the cardiac output per minute (COM). At decreasing pO_2 in the surrounding medium, the amount of /104 oxygen delivered by the blood in 1 min to the tissues depends both on the variations in the COM and on the variations in oxygen level of the arterial blood.

Thus, the value of the COM enters as a component in all indices characterizing the oxygen-transport function of the circulation, its intensity, effectiveness, and economy. A comparative analysis of these indices can be used both for the age-related characterization of the role of hemodynamics in the regulation of oxygen utilization (OU) and for conditions of hypoxia.

A quantitative approach to the evaluation of the role of hemodynamics in the regulation of the oxygen regime in animals of different age groups can be illustrated by our experimental data obtained in collaboration with N.V.Lauer, A.Z.Kolchinskaya, V.V.Turanov, M.M.Seredenko on dogs of medium age and on puppies under conditions of normal oxygen content in the inspired air and of inhalation of hypoxic mixtures.

A comparison of the conditions of arterialization and deoxygenation of blood in dogs of middle age and in 3 week old puppies has shown that the arteriovenous gradient of pO_2 is higher in the puppy than in the adult dogs since, because of the more intense oxygen consumption of the puppy tissues, the pO_2 of the venous blood is considerably lower than in adult dogs. The arteriovenous

gradient shows practically no difference from that of adult dogs. This can be explained by the higher velocity of circulation in puppies, decreasing the /105
arteriovenous difference and compensated by the more intense oxygen consumption. The oxygen capacity (OC) of the blood in very young puppies is lower than in the blood of adult dogs and, despite the high oxygen level of the arterial blood, is still lower in vol.% than in middle age.

The above-described conditions of arterialization of the blood in the lungs and oxygen consumption of the tissues are likewise factors that determine the blood circulation as well as the amount of oxygen delivered in unit time to the tissues.

A comparison of the amount of oxygen, delivered to the tissues in unit time by the blood (qO_2a) in adult dogs and in 3 week old puppies, indicates the natural rise in this value with age. However, a comparison of the intensity of the oxygen-transport function of hemodynamics in adult dogs and in puppies shows that, in puppies, the COM and the amount of oxygen delivered per kilogram of body weight per minute is greater than in adult dogs, so that the intensity is also higher.

To some extent, the efficiency of the oxygen-transport function of hemodynamics can be estimated from the interrelations between the amount of oxygen delivered by the blood to the tissues and the amount of oxygen consumed by the latter. A comparison of the effectiveness of the oxygen-transport function in puppies and adult dogs indicates the higher effectiveness of the blood stream in puppies; in adult dogs, the blood stream, in unit time, delivers four times as much oxygen to the tissues as required, while it delivers only twice as much in the case of puppies.

A certain idea as to the economy of the oxygen-transport function of /106
the blood can be obtained from the value of the hemodynamic equivalent, which indicates the quantity of blood required for the consumption of one liter of oxygen. The hemodynamic equivalent in medium-age animals and in puppies lies approximately in the same range. This is explained by the fact that, in puppies with their more intense blood flow, the oxygen consumption of the tissues is also higher than in adult dogs, so that the ratio between these two values changes only slightly.

Another quantity which, to a certain extent, may characterize the economy of hemodynamics in its function of carrying oxygen to the tissues, is the oxygen pulse or, in other words, the oxygen efficiency of the ejection period (the ratio of oxygen consumption per minute to the heart rate). The oxygen effectiveness of the sphygmic period increases with age, since the heart rate slows on aging.

A quantitative analysis of the role of hemodynamics in the regulation of the oxygen regime indicates that, during the early stages of life, hemodynamics plays a special role in satisfying the high oxygen demand of the tissues. Despite the relatively low oxygen capacity of the blood, the delivery of oxygen to the tissues by means of a stepped-up and effective circulation completely meets the large oxygen requirements of the tissues at this age.

Under the conditions of oxygen deficiency, the role of the functional systems in the OU regulation is even more distinct. With varying pO_2 in the atmosphere, a complex of compensatory reactions appears in the organism, so as to maintain the oxygen consumption, as far as possible, at or near the original level. Studies on human subjects and animals have shown that the circula- /107 tory system responds to a fall in pO_2 of the ambient medium by an acceleration of the pulse, by increase in minute volume, and by a slight rise in blood pressure (Dripps and Comroe, 1947; Grol'man, 1932; Lutz and Schneider, 1919; Opitz, 1950; Asmussen and Chiodi, 1941; Rahn and Otis, 1947; Yegorov, 1941; Albers and Juzinger, 1956; Harrison and Blalock, 1927; Nagaya and others, 1954; Baird, Böhm and Howell, 1953; Gorlin and Lewis, 1954; Harliman and Wiggers, 1953; Leuzen and DeMaistre, 1954; Stroud and Conn, 1954; Stroud and Rahn, 1953; Bazilevich and Turovets, 1938; Shik et al., 1940; and many others).

However, despite the large number of investigations made, the literature does not answer the question as to what causes the organism to increase the blood circulation, in the sense of increasing the oxygen supply. We have attempted to do this, using data obtained at the Laboratory of N.V.Lauer on dogs under chloralose narcosis, subjected to increasing acute hypoxia.

As an example, let us consider the reaction of hemodynamics in the medium-age dog No.17, in which hypoxic gas mixtures (16.2%, 12.7%, 9.6%, 7.5%, 5,5% oxygen in nitrogen) were administered. As soon as a ratio of 16.2% O_2 was reached (P_1O_2 = 119 mm Hg) the COM already increased to 210 mℓ. This increase was due to the increase of the systolic output, since the pulse rate did not change. Such a higher COM provided the body with an additional 17 mℓ of oxygen per minute, leading to a somewhat greater oxygen consumption. A further decrease in pO_2 in the inspired air was accompanied by a further drop in oxygen level of the arterial blood and an increase in COM. On inhalation of a gas /108 mixture with 12.7% O_2 (P_1O_2 = 95 mm Hg), the COM increased by a further 190 mℓ, but this resulted only in an additional 7 mℓ oxygen. On continuing drop in the partial oxygen pressure, although the COM remained at a high level for a certain period of time (because of the reaction of pulse acceleration), the amount of oxygen delivered per minute by the blood to the tissues already declined to 57 mℓ/min which, at the almost unchanged level of oxygen consumption, suggests a disturbance of the equilibrium between supply and consumption of oxygen. A fall in P_1O_2 to 45 mm Hg causes an upward jump in COM. Thus, the sharp decrease in the oxygen level of the arterial blood makes this extreme stress of hemodynamics incapable of increasing the oxygen supply.

The significance of the increase in COM in hypoxia can also be estimated by a factor showing how many times the increase in COM increases the oxygen carried by the blood to the tissues in unit time, as hypoxia progresses. In the experiments discussed here, the qO_2a was 244 mℓ O_2 for inhalation of normal air. As soon as the P_1O_2 declined to 95 mm Hg, the value of qO_2a reached 260 mℓ, i.e., was somewhat above the initial level. This was due to the rise in COM. If it had not been for this rise, then the qO_2a at this P_1O_2 would have been only 193 mℓ. Thus, an increase in the volume of blood in the circulation increased the supply of oxygen to the tissues, despite the developing hypoxemia, by a factor of 1.3, which helped to maintain the supply of oxygen to the tissues at a level close to its original value.

Puppies, at an early age, lack the reaction of compensatory intensifi- /109
cation of functions in hypoxia. At normal pO_2 in the inspired air, both COM and qO_2a show maximum values; as hypoxia develops further, pulse rate, blood pressure, and COM decline gradually, correlating with the observed decline in oxygen consumption by the tissues in hypoxia (N.V.Lauer, 1959, and others).

Based on the above examples, we attempted to answer the question as to the factors that are able to intensify the circulatory function in hypoxia, so as to maintain the assigned values of the parameters of oxygen utilization. We have seen that, in itself, an intensification of function yields no information on the effectiveness of the adaptive reaction, and only an evaluation of the amount of additional oxygen produced by an intensification of function will yield an answer to the question whether the dynamic equilibrium between demand and supply of oxygen to the tissues is maintained or impaired.

THE REGULATION OF THE OXYGEN REGIME /110

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The concept that oxygen exchange in the body is regulated dates back to the discovery of the energetic role of oxygen in physiological processes and to the experimental proof of its participation in maintaining life and varying the functions of the physiological system of the organism (Baire, 1878), all of which are discoveries which radically modified the ideas of respiration that were then commonly accepted.

Within wide limits, oxidation does not depend on the rate of oxygen supply through the blood but on the physiological demands of the body (Pflüger) and is regulated with amazing accuracy in accordance with the amount of energy consumed by the organism (Rubner, 1908). These findings suggested that the oxygen demand of the tissues was the factor controlling its delivery to there.

Respiration, in the broad sense of the word, began to be considered as a multistage process, essentially oxidation, with the fundamental mission of controlling the supply of oxygen to the organism and the removal of carbon dioxide from it, in accordance with physiological requirements (Haldane, 1922).

However, despite the general recognition that the physiological requirements operate as the controlling factor, the trend of development taken by the concepts on regulation of respiration, circulation, and the red blood system, supplying oxygen to the tissues, tended rather to consider these regulatory /111 mechanisms by themselves, artificially and schematically detached from the demands of the metabolism.

There can be no doubt that the extensive progress obtained in a relatively short time by the doctrine of reflex and humoral regulation of respiration and circulation; the accumulation of evidence on the fine anatomical and functional interrelations of the central and peripheral nervous structures participating in the regulation of the physical functions; the intimate mechanisms of these interrelations; the action of various chemical agents, including oxygen and carbon dioxide, on the central and peripheral nervous structures; all of these laid a firm foundation for the idea of the automatic control of physiological functions.

The discovery of the chemoreceptors of the carotid and aortal sinuses as the major regulators of respiration and circulation; the advances made by the doctrine of chemoreception as a whole; the discovery of the chemoreceptors of the venous bed and of the tissue chemoreceptors, all strongly confirm the participation of chemical agents in the regulation of respiration and circulation.

The role of oxygen in the regulation of respiration and circulation began to be recognized in Rosenthal's time. He stipulated the existence of what we

know today as feedback in automatic control theory, between the oxygen saturation of the arterial blood and respiration.

The discovery by Hering, Anichkov, Moiseyev, Heymans, and others of reflexes to respiration from the chemoreceptors of the carotid and aortic sinuses, the electrophysiological proofs of the action of the p_aO_2 on these receptors /112 (Heymans, Ryland, Bock, Stella, Euler, Sotterman, Witzlöb, Bartels, Budde, Mochizuki and others) and the proof of the exceptional role of the chemoreceptors of just these carotid and aortic zones in the regulation of external respiration in hypoxia (Asmussen, Chiodi, Marshak, Ardashnikova, Shik, Kulik, and others) confirm the idea that oxygen plays a role in the reflex self-regulation of respiration, not only in hypoxia but also at normal oxygen content of the inspired air.

Many studies have shown that the oxygen parameters over the entire path of the oxygen exchange in the organism possess a regulating influence on the systems supplying oxygen to the tissues, i.e., that it is not only the partial oxygen pressure in the arterial blood but also the P_IO_2 (the partial oxygen pressure in the inspired air, in the alveoli, the oxygen tension in the venous blood, and apparently also in the tissues) that exert a control action on the functional systems supplying oxygen to the tissues.

Ever since Pflüger and Domen (1868) showed that an excess of CO_2, if not too great, has the same effect as an oxygen deficiency in exciting the respiratory center, and ever since Michet-Ruche (1885) showed in an experiment with human subjects that a slight increase in CO_2 in the air intensifies respiration while a similar decrease in oxygen does not stimulate it, i.e., that the chemical regulation of respiration is determined by the CO_2 content of the air rather than by oxygen content, carbon dioxide and oxygen have been rivals for recognition as regulators of respiration.

The existence of CO_2 reflexes in the lungs themselves, as predicted by /113 Donders and Rosenthal who postulated that CO_2 could excite special chemoreceptors located in the alveoli, was convincingly demonstrated by Pi Suner (1947) who observed the appearance of a reflex of asphyxia to an increased CO_2 concentration directly from the alveoli.

Thanks to the work by Haldane and his school, the role of CO_2 in the regulation of respiration began to be recognized as the dominant element, and the concept of the direct central action of CO_2 and hydrogen ions was adhered to for many years.

Based on the studies by Haldane and coworkers, the humoral theory of respiratory regulation became widespread. According to this theory, the changes in respiration arise primarily from changes in the CO_2 tension of the alveolar air and thus in the arterial blood, directly or through the pH of the blood, which exerts an influence on the respiratory center.

Subsequently, however, Haldane found certain other facts which made him abandon the strict concept of this relationship. First of all, the role of CO_2 as the controlling factor in respiratory regulation became somewhat doubtful due to results from experimental hypoxia, when respiration was intensified on a decrease of CO_2 in the arterial blood (Fitzgerald, Königheim, Cormack, and others)

and from cases of physical stress, when the respiration increased manifold, while the CO_2 level of the arterial blood remained almost constant. This /114 made many authors aware of the fact that the concept of the humoral action of the blood pCO_2 and pH was unsatisfactory.

Nevertheless, even today, CO_2 still is believed to have the dominating influence in the regulation of respiration. Thus, even in very recent work on the mathematical simulation of the external respiration, the pCO_2 of the arterial blood is considered to be the main controlled parameter (Grey, 1945-1956; Grodins and James, 1963; Yamamoto, 1963; Defar, 1963; Florenten, 1964). Although the idea that the pCO_2 of the arterial blood is the controlled parameter must be abandoned, many experiments on simulation of breathing under physical stress are still made to prove that changes in the p_aCO_2 during the respiratory cycle have a regulating effect on the respiration.

Excessive specialization has led to the study of function as a self-sufficient process. This in turn has resulted in detailed investigations of the nervous and humoral regulation of respiration, circulation, etc. which, while yielding many valuable data on the structural and functional mechanisms of regulation, distracted the attention of physiologists from the basic purpose of regulation, namely, that of supplying the physiological needs of the organism.

Thus, in considering the oxygen metabolism, the control of the oxygen level at each stage was disregarded, while the control of the functions of the physiological oxygen-carrying systems was studied separately from the quantitative indices of oxygen metabolism.

The approach to the oxygen metabolism, as a process taking place under a definite regime and characterized by the relevant combination of the oxygen /115 parameters at each stage, automatically led to the conclusion that the regulation of the oxygen regime of the organism is automatic, being ruled by numerous physiological, reflex, humoral, physical, physicochemical, and biochemical influences on the oxygen parameters.

The events taking place during this process may be regarded as processes in a complex automatic control system, whose purpose is to ensure continuous matching of the amount of supplied oxygen to the oxygen demand of the tissues at any instant.

The regulation of this system concerns the individual stages of oxygen delivery to the tissues, responsible for the transport of oxygen from the ambient air (concentrator) to the tissues (consumer). The controls are represented by the regulatory mechanisms of external respiration, the regulators of hemodynamics, and the mechanisms regulating the oxygen capacity of the blood.

The controlled parameters at the output of the system as a whole are the oxygen parameters of the venous blood: the quantity of oxygen transported by the venous blood in unit time (q_vO_2), and the partial oxygen pressure in the venous blood (p_vO_2), since maintenance of certain values of these parameters ensures the necessary level of oxygen consumption by the tissues and since any changes in these parameters reflect the amount of oxygen consumed by the tissues at each given instant.

Under stable conditions, when a material and energy balance is observed, /116 i.e., when the amount of oxygen delivered corresponds to the oxygen demand of the tissues as predetermined by phylogenesis and ontogenesis for a given state of the organism, the current value of the controlled parameters coincides with the assigned value; in particular, the $p_v O_2$ will be 37 - 40 mm Hg, and $q_v O_2 = q_a O_2 - q_t O_2$.

In the case of disorders leading to a decrease in oxygen supply to the tissues, such as variation in pO_2 of the inspired air, systemic disturbances (hypoxic, hemic, circulatory types of hypoxia), or variation in the stress on the oxygen demand system of the tissues (for example, in physical work), a mismatch is created between the actual and assigned values of the controlled parameters ($p_v O_2$ and $q_v O_2$). Information on this mismatch is fed to the input of the regulators of which the most important are those that regulate ventilation, circulation, oxygen capacity of the blood and which, by control exerted on the system of MV, AV, CO (minute ventilation, alveolar ventilation, cardiac output), hemoglobin minute volume, etc., produce a decrease of the mismatch between actual and assigned values of the controlled quantities.

Since the changes in the $p_v O_2$ are proportional to the change in $q_v O_2$, it may be considered that information on the change in $q_v O_2$ is transmitted to the sensing receptors of changes in $p_v O_2$.

Thus, a closed loop control is effected with respect to the parameters $p_v O_2$ and $q_v O_2$ (Fig.1).

The stress characteristic $q_v O_2 = \delta(q_t O_2)$ is represented in the form of /117 an inclined straight line: With increasing stress, the value of the controlled parameter declines. If there were no system regulators that maintain the controlled parameters at the prescribed levels, then the oxygen level of the venous blood would already drop to zero at a stress only 2.1 times as great as the nominal, in a healthy person. This would take place because, in a person of middle age, the venous blood transports only 2.1 times as much oxygen per minute as is consumed.

The existence of a control system ensures maintenance of $q_v O_2$ at a level close to its initial value.

The control characteristics are represented by the dependence of the controlled parameter $q_v O_2$ on the control influences MV and CO. The characteristic of the dependence of $q_v O_2$ on CO will be a straight line inclined to the abscissa axis by the angle α, where $\tan \alpha = \frac{q_v O_2}{Q}$, i.e., the oxygen level of the venous blood. At constant stress, the limits of displacement of the control characteristic will be from $\tan \alpha = 18$ to 6, and have an angle α from 87 to 81° (for hyperoxic states, $\tan \alpha = 18 - 14$, $\alpha = 87 - 86°$; for normoxic states, $\tan \alpha = 14 - 10$, $\alpha = 86 - 85°$; and for hypoxic states, up to an altitude of 8000 m, $\tan \alpha = 10 - 6$, $\alpha = 85 - 81°$).

Under varying stress, the control characteristic is displaced parallel to itself.

The control characteristic of the dependence of $q_v O_2$ on MV, at constancy /118 of the other control actions, is expressed by an exponent asymptotically approaching its maximum value, which is $q_a O_2$.

Data resulting from experimental studies on human subjects at various altitudes in the mountains have confirmed the theoretical assumptions as to the shape of the curve of the control characteristic for the dependence of $q_v O_2$ on MV.

An additional control according to a second principle, i.e., load regulation effected by the SROS (self-regulating oxygen system) considerably increases the reliability of the system and the accuracy of maintenance of the controlled parameters.

The load or stress in our system is represented by the oxygen consumption of the tissues. The amount of CO_2 excreted increases proportionally to the oxygen consumption, although CO_2 is not itself a direct product of the oxidation reaction but can serve as a measure of oxygen consumption by the tissues. This is convincingly indicated by these studies of oxygen consumption and CO_2 liberation with increasing intensity of physical work shown in Fig.5. Thus, the changes in the amount of CO_2 removed by the venous blood from the tissues and the $p_v CO_2$ may serve as satisfactory indicators of the changes in oxygen consumption, i.e., of the variations in load on the system as a whole.

Load control is accomplished in an open system, where the starting stimulus is the variation in load rather than the deviation of the controlled parameter from its assigned value. Thus, under certain regimes, there will be an over- /119 control during which an increase in the load will only increase the value of the controlled parameter. A striking example of load control is the control of the oxygen parameters during physical work of varying intensity. Simultaneously with an increase in oxygen consumption, the $q_v CO_2$ will also increase. The influence of this increase on the controls will lead to an increase in the MV, a better oxygen saturation of the arterial blood, an increase in cardiac output and thus in $q_v O_2$. In this case, notwithstanding the increasing oxygen consumption, $q_v O_2$ may not only fail to decline but may even increase. This will happen because, if the percentage increase in oxygen consumption is greater than the percentage increase in cardiac output, then the absolute increment in cardiac output and the greater increment in $q_v O_2$ due to the greater absolute values of cardiac output will exceed the absolute values of the oxygen consumption increment. Thus, in physical work that increases the consumption by a factor of 10, from 200 ml to 2000 ml of oxygen, the cardiac output will increase 2.9 times. At the same time $q_a O_2$ will increase from 1000 ml of oxygen to 2900 ml, and $q_v O_2$ will rise from 800 ml to 900 ml. (The calculations are based on data by Christensen.)

In most situations of life, both these principles of regulation of the oxygen regime are realized, namely, regulation by the oxygen parameters and regulation load, i.e., control by the CO_2 parameters. However, some cases are encountered when one of these control loops participates very little in the work of the system; in these cases, control is effected primarily by the other loop. For example, on inhalation of CO_2 which simulates a load without increasing /120 the oxygen consumption which could have lowered the $q_v O_2$, only the load control

is switched on.

On the other hand, in hypoxia when the oxygen parameters decline while the consumption remains practically constant and the q_vO_2 declines owing to the leaching of CO_2, the loop of control by parameters takes over the control function.

Above, we discussed the principles of regulation of the oxygen regime of the organism. The next question is that of the structural organization providing such an exact regulation of the oxygen regime on the basis of the above principles.

The self-regulating oxygen system (SROS) obviously is a system consisting of three series-connected elements or stages included in feedback loops. In each of these elements (in the lung reservoir, the blood reservoir of the lung capillaries, and the blood reservoir of the tissue capillaries), the output parameter, which is the input for the next stage, is controlled. Thus, each stage is an independent system in which both input and output parameters are controlled, making the system highly reliable.

The system as a whole and its individual stages are served by three main regulators, which are interconnected: respiratory regulator, circulatory regulator, and regulator for the hemoglobin circulating in the blood.

The input of the first stage is fed with the amount of oxygen determined by the minute volume and with the p_1O_2 arriving through the concentrator from /121
the ambient air. As a result of the transformation at the output of the stage, there is alveolar ventilation and p_AO_2. In spite of the cyclic and discontinuous character of the oxygen supply from the ambient air and the continuous delivery of oxygen into the blood of the pulmonary capillaries, the quantity p_AO_2 remains amazingly constant under normal conditions (Sechenov). This exact control of the parameter p_AO_2 is due to the fact that an increase in the volume of the lung reservoir involves an increase in the quantity of oxygen input. In this case, the oxygen concentration in the alveolar air will be constant, since the system by which the contractions of the respiratory musculature follow the volume of the reservoir (the Hering-Breuer reflex) maintains a definite ratio between respiratory volume and size of the reservoir. It is entirely likely that there is a feedback between the chemoreceptors of the nose and upper respiratory tract reacting to variations in the partial oxygen pressure of the ambient air, and the receptors of the alveoli transmitting information on the variation in p_AO_2 to the respiratory regulator. Thus, the oxygen parameters of the alveolar air are controlled even in the first stage, although - as shown below - the chemoreceptors of the carotid and aortic sinuses play a considerably greater part in their regulation.

The output from the first stage, i.e., the alveolar ventilation ($\dot{V}_A$) with a definite partial oxygen pressure of the alveolar air (p_AO_2) and a definite /122
amount of oxygen transported by the venous blood, is fed to the input of the second stage which is the reservoir of the lung capillaries. The output from this stage, as a result of the transformation of the input parameters under the action of alveolar ventilation, the flow of blood through the lungs, and the rate of diffusion of the oxygen-binding properties of hemoglobin, is fed with

oxygen parameters of the arterial blood, p_aO_2 and q_aO_2. We must emphasize the fact that one of the input parameters of the second stage, q_vO_2, is the principal controlled parameter of the entire system. Feeding it to the input of the second stage has a stabilizing effect on the function of the second and third stages and thus of the system as a whole in view of the fact that, in the second stage, there is not only a regulation by the output parameter p_vO_2 but also a regulation by disturbing influences, leading to a variation in the input parameter of the second stage (q_vO_2). Information on the variation in q_vO_2, transmitted to the chemoreceptors of the venous bed over the variations in p_vO_2, actuate the respiratory and circulatory regulators which begin to operate before the changed q_vO_2 reaches the input of the second stage, thus preventing the appearance of this change at that input. This preventive measure is reliable, since the delay time of the q_vO_2 on the route from the output of the third stage to the input of the second stage, determined by the rate of flow in the veins on the segment between right heart and lung capillaries, is considerably longer than the delay in the feedback of the regulators; this depends on the rate of transfer of nervous impulses from the receptors of the right heart, that receive information on the variations in p_vO_2, to the nerve centers and back to the effector organ of the circulatory regulator.

In addition, the action of p_vO_2 on the respiratory regulator reorganizes /123 the mechanisms of the first stage (increasing the alveolar ventilation), thus preparing for the reception of the changed q_vO_2. The alveolar ventilation still retains the function of subregulation in the case of disturbing influences on the system operating under the conditions of the given steady state.

Thus, there is regulation of the output (controlled) parameter q_aO_2 and p_aO_2 of the second stage by the disturbance of q_vO_2 at its input.

The output parameter of this stage, p_aO_2, is the controlled parameter for the first two stages. Its deviations from the assigned value, reaching the input of all three regulators, result in the appearance of control actions by the respiratory regulator at the input of the first stage and by the regulators of circulation and of oxygen-binding property of the blood, at the input of the second stage. Thus, there are two principal feedback loops; one embraces the second stage, and the other the first and second stages. Our assertion that the p_aO_2 is the main controlled parameter at the output of the second stage is confirmed by the fact that even minor deviations of this parameter from the assigned value (100 mm Hg) cause the control mechanisms to attempt to restore the previous level.

Thus, accurately regulated values of p_aO_2 and q_aO_2 are fed to the input of the third stage. After passing through transformations in the third stage, that consist essentially in the delivery of oxygen to the tissues, these parameters leave the third stage in the form of the venous blood parameters, p_vO_2 and /124 q_vC_2.

Let us consider examples of the operation of the system.

Example 1. The oxygen demand of the tissues has increased (this is equivalent to what one calls an increase in load in the terminology used in the theory of automatic control). At the initial instant, at constant blood flow into the

tissues, the pO_2 and the oxygen level of the venous blood both decrease, in accordance with the amount of oxygen extracted by the tissues from the blood. The considerably suboxygenated venous blood must extract greater amounts of oxygen from the alveoli, which may be accomplished in two ways:

a) In the absence of variations in pulmonary function and circulation, the arterial blood will be partially suboxygenated. The decrease in the pO_2 of the arterial blood causes: 1) intensified bioelectric activity of the chemoreceptors of the carotid and aortic zones; 2) variation in the bioelectric activity of the cells of the respiratory center. Thus, information on the decrease in the pO_2 of the arterial blood reaches the nerve centers, where it is transformed into control signals to the working organs, the respiratory musculature, the heart, and the smooth musculature of the blood vessels, the variation in whose activity corresponds to the optimum saturation of the venous blood and the elimination of the created mismatch.

b) Information on the decline in the pO_2 of the venous blood can be transmitted to the respiratory and vasomotor centers by the variation in bioelectric activity of the chemoreceptors of the major veins, the right precordium, and the pulmonary artery. Although no convincing experimental proofs exist for this /125 route, there is also no valid reason for rejecting this possible regulation, the more so since the literature contains references to the existence of chemoreceptors in these blood vessels, including very recent references to the role of the pO_2 of the venous blood in the regulation of cardiac output (L.L.Shik, 1964).

c) The mismatch between the oxygen demand of individual tissues and its supply can be eliminated within the limits of the last stage of the self-regulating oxygen system. According to recent data, the decline in pO_2 in the arterial blood relaxes the precapillary sphincter in the area of the tissue supplied by the capillary, leading to a dilatation of the capillary and an intensification of blood supply, i.e., to an automatic delivery of oxygen to the tissues (Hayton, Ross, Carrier, Walker, 1964; Bern, 1964).

Load control by CO_2, as described above, is used as a supplementary control in the first case.

Example 2. The pO_2 at the input to the system was decreased (variation of the input parameter). As a result of the undersaturation of the hemoglobin with oxygen, the pO_2 of the arterial blood declines, and information on this decline is transmitted to the respiratory center. This closes a feedback loop within the first two stages. If this is insufficient, the tissues, even at the initial instant and to satisfy their unchanged requirements, will extract the same amount of oxygen from the blood; because of the decreased delivery of O_2, the pO_2 of the venous blood will then be lower than usual. Regulation can be accomplished in the above-described manner. However, as noted before, the organism has highly efficient measuring and regulating devices to preclude any possibility of insufficient oxygen supply to the tissues and to ensure them of optimum conditions for oxygen utilization (higher pO_2 of the blood washing the tissues); these are the chemoreceptors of the sinocarotid and the aortic regions, whose intensification in bioelectric activity can be recorded even for decreases as little/126 as 2 mm Hg in the pO_2 of the arterial blood, namely, from 100 to 98 mm Hg (Euler,

Liljestrand and Sotterman, 1939; Alvarez-Bouhuys, 1953; Witzlöb, Bartels, Budde, Mochizuki, 1955; Wintzler, 1955).

The information on the decrease of P_{O_2} in the arterial blood, transformed in the centers into control signals, is transmitted to the effector organs which are then triggered to eliminate the mismatch.

The proposed scheme of the automatic oxygen regulation system discloses the possibility of mathematical simulation, establishing the general laws and properties of the regulation of the oxygen regime.

We present briefly only the most general ideas, far from complete, on the possibility of automatic regulation of the oxygen metabolism in the organism. The complexity of the problem, the inadequate study of neurohumoral regulation of the functions in the organism, and the restriction of the exposition by the scope of the assigned theme, make it more difficult to give, at this stage, a more detailed analysis of the system of automatic regulation of the oxygen regime of the organism. However, it seems that an application of the automatic control concept to the study of the oxygen metabolism regulation may make it easier to understand the economy and reliability of regulation in the organism.

MODERN CONCEPTS ON THE REGULATION OF EXTERNAL RESPIRATION /127

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Although it is recognized as obvious that pulmonary ventilation is the result and the measure of respiratory activity which, by nerve or chemical reflex mechanisms, is made to correspond to the needs of the organism, most authors separate this from the fundamental problem in studies of the nervous and humoral regulation of respiration, mainly because of the narrow specialization of their research.

Owing to the advances in neurophysiology and the use of highly refined methods of electrophysiological research, extremely valuable information has been obtained on peripheral and central mechanisms responsible for the reflex and humoral regulation of respiratory movements and constituting the sensing systems and on the systems that process information and transmit it to the effector organs of the regulator; these data permit formulation of very general preliminary ideas on the structure of the respiratory regulator.

During the past two decades, new data have been obtained on the localization of the respiratory centers in the medulla oblongata and the pons, on the structures of the upper part of the brain stem participating in the regulation of respiration, on the cortical and cerebellar influences on respiration, permitting insight into the mechanisms of rhythmic respiration and the internal mechanisms of variation of the basic respiratory rhythm, and evaluation of the role of the vagal proprioceptive and chemoceptive control, and the role of the carotid and aortic chemoceptor zones in the regulation of pulmonary ventila- /128
tion.

Ideas are being developed on the respiratory regulator as a feedback system in which, on the one hand, the dependence of the controlled parameters, the p_aCO_2 of the arterial blood and the p_aO_2, on the pulmonary ventilation (equation of the object), and, on the other hand, the dependence of the pulmonary ventilation on the arterial pCO_2, pH, pO_2 on variation of these parameters at the input to the system (the Grey hemostat, 1945) and the parameters of variation of the metabolic rate, are fed back to the input of the system (Grodins and James, 1963); mathematical models for the regulation of respiration are now being proposed (Defar and Florenten, 1963). These authors attribute the decisive role in regulation of respiration to CO_2, although many others are convinced that the mechanisms which exert control over CO_2 are far from being clear.

The authors note the absence of any unified conception which could properly explain the regulation mechanism of external respiration under various conditions, such as hypoxia, muscular stress, etc. (Marshak, 1961; Schmidt, 1963; Fishman, 1963).

The weak point in modern concepts on respiratory regulation is the assump-

tion that the latter is limited to a closed loop composed of ventilation - chemical composition of arterial blood - ventilation.

In our opinion, the extension of the control loop to include a stage that reflects the oxygen consumption by the tissues and the production of CO_2 and other metabolites, with allowance for the factors participating in the regulation of the oxygen parameters in all stages of oxygen metabolism in the organism could help to establish more exact ideas on the regulation of external respiration.

THE PROBLEM OF OXYGEN RESERVES IN ANIMAL AND HUMAN ORGANISMS /129

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At all stages of evolution in the animal world, the well-being of the organisms was ensured by the formation of reserves of vital materials, such as fats, carbohydrates, salts, and other substances necessary to maintain the normal metabolic level.

The extremely important element oxygen, without which the higher organisms - including man - cannot exist for longer than 1 - 2 min, is an exception in this respect. One would think that the establishment of reserves of this vital element would have been one of the major tasks of evolution. However, it is a fact that, over almost the entire history of evolution of the animal world, nature has not established significant reserves of oxygen in the animal organism.

A comparative study of the physiology and biochemistry of respiration has shown that, despite the multiplicity of structural formations that ensure supply of oxygen to the cells and tissues of the organism in various stages of individual development, the continuous supply of oxygen has always been maintained without significant reserves. In particular, throughout the history of development of vertebrates, there has been a substantial increase in the capabilities of the oxygen-supplying mechanisms, particularly with respect to the organs of aeration and hemodynamics which reach their highest efficiency in birds and animals. There is a sharp increase in the activity of hemoglobin-producing centers, such as the bone marrow and the striped musculature; nevertheless, /130 the oxygen reserves of the organisms are so minimal that an elimination of external respiration, i.e., of the supply of oxygen to the organism, can be tolerated for no more than 1 - 2 min.

The only exceptions are aquatic mammals and birds (whales, seals, penguins, seagulls, etc.), since they have the power to shut off external respiration for a long time, measured in minutes or tens of minutes, as is the case for the large cetaceans.

Apparently, there were fundamental causes which, in all stages of vertebrate phylogenesis, prevented the establishment of substantial oxygen reserves in the organism, except for a small group of animals which could secondarily revert to a watery habitat (aquatic mammals and birds). Until recently, biologists have been unable to give a convincing explanation of this paradoxical phenomenon.

Today, it is possible to give a rational explanation of this peculiarity of animal organisms. This is based on the discovery by Professor A.L.Chizhevskiy, as far back as the middle of the 1920's, to the effect that not only the chemical composition of the air but also its physical state is of vital importance for the organism.

One of the most important features of this physical state of the air is its definite saturation with electric charges, i.e., negative charges, owing to which the oxygen molecules pass into the ionized state. It has been shown that, if there is no ionized oxygen of negative polarity in the air, all experimental animals die rather rapidly. These studies by Professor Chizhevskiy shed light on the causes for the absence of significant oxygen reserves in the animal organism. /131

The underlying principle is simply that ionized oxygen exists for a very short time, of the order of several minutes, after which it loses its charge and is converted into the inert form. It is precisely for this reason that the animal organism is unable to build substantial reserves of ionized oxygen of negative polarity. However, oxygen molecules without a negative electric charge, as shown by Chizhevskiy's experiments, are unable to support normal animal life.

It should be borne in mind that the negatively charged oxygen ion, having nine electrons, resembles fluorine; however, on ionization of the oxygen, the spin of its nucleus is reversed. Apparently, the extremely fine physical phenomena that take place on the electronic and nuclear level, have played a decisive role in the evolution of the animal world, as a result of which, even the higher representatives of the vertebrates have no substantial reserves of oxygen.

The establishment of this fact is not merely of theoretical importance but also of great practical importance. As Chizhevskiy correctly says, "in building his dwelling, man deprives himself of normal ionized air". Indeed, within buildings and apartments inhabited by human beings, as Chizhevskiy has shown, the number of oxygen ions drops to a minimum; instead of the 500 - 600 ions per cubic centimeter of air under natural conditions, it goes as low as 15 - 20. Yet man spends more than half of his life inside buildings, and consequently breathes nonionized air. This is one of the main factors detrimental to human health.

The development of specific measures designed to improve the electric condition of the air of inhabited rooms is one of the most urgent problems of the near future. /132

OXYGEN TENSION IN CARDIAC MUSCLE AND BLOOD, UNDER CONDITIONS OF CIRCULATORY AND ANEMIC HYPOXIA

/133

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1. We determined the pO_2 in the cardiac muscle, the pO_2 and pCO_2 (in absolute units) in the arterial and mixed venous blood, the total respiratory metabolism and blood gas content, cardiac output, arterial pressure, and ECG in dog experiments. Circulatory hypoxia was induced by severe bloodletting and anemic hypoxia by replacing the lost blood with polyglucine.

2. At the peak of blood loss, the arterial pressure dropped to 0 - 10 mm, the pO_2 in the myocardium decreased to about 50% of its initial value, the pO_2 in the arterial blood declined slightly from 94 to 80 mm (87% of the initial value), and that in the venous blood from 46 to 23 mm (50% of the initial value). In the arterial blood, the pCO_2 tended to decline (32 mm initial and 27 mm at the height of blood loss) but increased in the venous blood from 45 to 75 mm (120% of initial). The arteriovenous difference in pCO_2 doubled. The oxygen consumption dropped considerably, and the cardiac output decreased. A decrease in the voltage of the ECG waves was noted, accompanied by various forms of conduction disturbances.

3. Immediately after replacement of the lost blood, anemic hypoxia developed: The oxygen capacity of the blood declined to half its value, the Hb content and the hematocrit index declined accordingly, the arterial pressure /134 was restored, and the cardiac output was about double the initial level. Under these conditions, the pO_2 in the myocardium returned to its initial value, and the pO_2 in the arterial blood approached its initial level; in the venous blood, it actually exceeded it (57 mm - 120%), which may have been due to the increased blood flow.

The pCO_2 in the arterial and venous blood returned to the initial level and oxygen consumption was restored. The ECG showed a restoration of the sinusoidal rhythm and of the amplitude of the waves.

4. Within two hours the cardiac output was higher than the initial level, although it showed a slight decrease by comparison with the preceding level, and the arterial pressure dropped somewhat.

The pO_2 in the myocardium continued to remain at its previous level; the pO_2 in the arterial and venous blood was close to the initial value. The arteriovenous difference in oxygen tension increased above the level it had at the end of replacement of the lost blood.

The pCO_2 was unchanged. Thus, in spite of the considerable decline in the oxygen capacity of the blood, the acute anemic hypoxia - judging by the myocardial oxygen tension and by the tension of the blood gases - was compensated.

NEW DATA ON FUNCTIONAL ORGANIZATION OF THE RESPIRATORY CENTER AND THE MECHANISMS OF COORDINATION OF RESPIRATORY MOVEMENTS

/135

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During the past decade, owing to the introduction of new methods of research (registration of the extra- and intracellular bioelectric potentials of the respiratory neurons, electromyography, use of new drugs, etc.), considerable progress has been made in the study of the functional organization of the respiratory center of the medulla oblongata and its afferent and efferent connections (Liljestrand, 1953, 1958; O.Wiss, 1954-1964; Baumgarten and Salmoreggi, 1960, 1961; Salmoreggi and Berns, 1960, 1961; Salmoreggi, 1962; Sergiyevskiy, 1959, 1961, 1964; Marshak, 1960, 1964; Euler et al., 1952, 1963; Oberholzer, 1952, 1960; Turner, 1954; Roytbak, 1952, 1959; Kocherga, 1958, 1961, 1963, 1964; Widdicombe, 1954, 1960, 1963; Waldman, 1963, 1964; Sirs, 1962, 1963, 1964; Glebovskiy, 1963, 1964; Sumi, 1963, 1964 and others).

A characteristic feature of the organization of the respiratory system is that its effector apparatus (the respiratory muscles) is connected with a somatic system related genetically to the locomotor musculature, and has afferent representation in various departments of the central nervous system, while the afferent influences on the respiratory center arrive primarily from the interceptors (carotid sinus, receptors of lung expansion, etc.) as well as directly through the blood. It is generally known that the respiratory muscles not only participate in maintaining the respiratory metabolism but also perform other functions (protective respiratory reflex, postural reflexes, formation of the rhythm of speech in man). It is still a controversial question whether all /136 forms of activity of the respiratory muscles depend on the flow of nervous impulses from the bulbar respiratory center, or whether the reflex influence on the spinal motoneurons of the respiratory muscles, located on the segmentary and supersegmentary levels, also play an important role in the development of these forms of muscular activity.

We conducted a systematic investigation of the activity of the respiratory muscles and the significance of the various departments of the central nervous system in the integration of their functions. We applied the methodological technique of simultaneous registration of the electric reactions of the respiratory and locomotor muscles (electromyography) to various functional states of the organism of the experimental animals (cats and dogs) and also to electric stimulation of various departments of the central nervous system (cerebral cortex and cerebellum) and of the afferent nerves.

During our study, we demonstrated the intimate connection between the phasic-tonic reactions of the locomotor and respiratory muscles and described certain features of the influence of the cerebral cortex, cerebellum, and reticular

formation of the brain stem on these reactions.

On electric stimulation of certain regions of the cerebral cortex, in accordance with the literature data (V.Ya.Danilevskiy, 1874; W.Smith, 1938; M.V. Sergiyevskiy et al., 1950, 1959, 1964; Turner, 1954 and others), we registered both stimulating and inhibitory effects on the respiratory muscles. These influences can be either corrective or starting.

Stimulation of the motor zones of the cerebral cortex (the region of /137 controlling the foreleg and trunk) was accompanied by changes of the phasic and tonic activity of the muscles of the forelegs and the respiratory muscles. The results of these experiments indicate the existence, in the spinal cord, of respiratory intermediate neurons able to perform various functions depending on their associations with the peripheral segmentary formations and the supersegmentary central structures. The existence of intermediate respiratory neurons was likewise confirmed by Pitts (1942) and Sumi (1963, 1964).

The type of our experiments and their results, together with certain literature data, lead to the conclusion that the cerebral cortex is not equipotential in its capability to modify respiration. On the one hand, by acting on the bulbar respiratory center, the cortex correlates respiration with the other vegetative functions of the organism; on the other hand, the motor zone of the cerebral cortex and the cerebellum participate in the regulation of the tonic function of the respiratory muscles and the correlation of respiratory movements with locomotor movements.

Thus, the influence of the central nervous system (cerebral cortex and cerebellum) on the respiratory muscles is accomplished not only over the functional structures of the bulbar respiratory center but also over the intermediate respiratory neuron of the spinal cord and the nervous formations regulating the tonic function of the respiratory muscles.

VARIATION IN TISSUE OXYGEN TENSION, IN DIRECT ISOLATED CORONARY PERFUSION

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Isolated direct coronary perfusion (terminal opening of the coronary arteries) was performed for an hour under conditions of hypothermia (blood temperature 20 - 24° C) at constant volume flow.

Various gas regimes of perfusion were used: oxygen, in which only oxygen was fed to the oxygenator; and oxygen-carbon dioxide, in which 3 - 5% of carbon dioxide was added to the oxygen for the oxygenator.

The experiments were run with and without coronary perfusion. We studied the variation in oxygen tension in the myocardium of the left ventricle and the skeletal muscle, using the polarography method.

During coronary perfusion with cold blood, using the oxygen method against a background of hypothermia, we observed an initial rise in myocardial pO_2 for 3 - 5 min by 30%, followed by a gradual decline by 10 - 15 %, although the pO_2 level was higher than the initial. A comparison of these indices with the pO_2 data of the myocardium under artificial blood circulation, at continuous oxygen regime under hypothermia without coronary perfusion when the myocardium pO_2 falls below its initial level, indicates a favorable action of coronary perfusion on maintenance of oxygen tension at a sufficient level.

Simultaneously, the oxygen consumption of the myocardium without coronary perfusion but with oxygen regime decreases whereas, with coronary perfusion, /139 it remains in the range of the initial level; this again suggests that the level of redox processes in the myocardium is higher during coronary perfusion (Ye.N. Ashcheulova).

The addition of 3 - 5% carbon dioxide during protracted hypothermal perfusion results in an increase in oxygen tension in the myocardium by only 25% above the initial level; with coronary perfusion, the pO_2 of the myocardium rises to double its initial level, and the coronary blood flow increases.

Consequently, coronary perfusion, even with oxygen regime, establishes better physiological conditions for the maintenance of viability of the myocardium; the use of an oxygen-carbon dioxide regime during coronary perfusion ensures optimum conditions for myocardial activity.

The oxygen tension in a comparable skeletal muscle declines less during

coronary perfusion than without it.

Besides this, the influence of CO_2 in accelerating the dissociation of oxyhemoglobin is very important in preventing myocardial hypoxia during hypothermal coronary perfusion under the oxygen-carbon dioxide regime.

The increase in oxygen tension of the myocardium in coronary perfusion depends on the initial level of the pO_2.

The addition of CO_2 to the oxygenated perfusion blood, in parallel perfusion, is an effective means of preventing hypoxia.

The level of the oxygen tension in the myocardium throughout coronary /140
perfusion, especially at its end, is of prognostic significance. At a high myocardial pO_2, as a rule, no hypoxic phase is observed on subsequent restoration of cardiac activity after warming.

ROLE OF THE CHEMORECEPTORS OF THE CAROTID SINUSES IN THE REGULATION OF PULMONARY RESPIRATION

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One of the principal characteristics of the living organism is its ability to maintain on a definite level, and within certain limits of deviation from the last level, the structure of the organs and tissues and the state of their metabolic processes, which as a whole ensures a relatively stable state of the complex system of the living organism. The stability of this system, under definite environmental conditions, is guaranteed by nervous and humoral regulatory mechanisms, coordinated by the central nervous system.

The regulatory functions of the CNS are accomplished by reception of information on the state and changes in the medium surrounding the organism and on the internal organs and tissues of the organism.

The sensor is the primary stage of any information system. It must be noted that the principal property of a sensor must necessarily be its selective sensitivity or its specific tendency to react to definite states and changes. The receptor apparatus plays the role of the sensorium in biological systems.

One of the important and specialized interoceptor mechanisms of the organism are the so-called chemoreceptors of the carotid reflexogenous zones located in the carotid body (glomus caroticum).

The most distinct and pronounced reaction to excitation of the carotid /142
chemoreceptors is the initiation of respiration. Excitation of these receptors also causes a number of other reflex reactions. Nevertheless, most researchers, in studying the function of the carotid gland, placed main emphasis on the respiratory excitation in evaluating the significance of this glomus for the organism. However, it was exactly the study of the role and participation of the carotid gland in this process that led to the main controversial questions on the mechanism of respiratory excitation in acute hypoxia and hypercapnia. This applies particularly to their role in the excitation of pulmonary respiration induced by carbon dioxide.

It is well known that pulmonary respiration has two aspects, namely, to supply the organism with oxygen and to remove carbon dioxide from it; under certain conditions, each of these aspects may become dominant. From this point of view, it evidently is primarily necessary to consider the carotid gland as information transmitter.

A number of authors have shown that an increase in the CO_2 tension of the blood and a corresponding decline in the pH of the blood induces excitation of the carotid gland and excitation of respiration. It has been found that, beginning at a certain level of the blood pCO_2 (about 30 mm Hg), there exists a linear relation between the CO_2 tension and the degree of excitation of the

carotid gland. It has also been found that, after ligation of the carotid gland, the pulmonary respiration is markedly depressed in animals and the CO_2 tension of the alveolar air is increased. This persists even if the animal is inhaling pure oxygen. It has also been shown that the carotid chemoreceptors react earlier than the respiratory center to an increase in CO_2 tension.

The velocity of the reaction is also a highly important feature of the /143
acid excitation of the carotid gland. The reaction takes place simultaneously with a shift in pH in the carotid gland toward the acid side and is rapidly stopped on elimination of the acid from the carotid gland.

On the basis of these data one can agree with numerous authors who state that the carotid gland participates in the regulation of normal respiration. It must be assumed that this regulation is effected through the mechanism of acid excitation of the carotid gland. Such excitation of the carotid chemoreceptors depends directly on the concentration of hydrogen ions and consequently also on the presence, and naturally also on the quantity, of acid products especially of carbon dioxide. This is determined, however, by the degree of pulmonary ventilation.

Bearing in mind that the pulmonary ventilation is of great importance in the regulation of the acidotic shift in the organism, we can consider the mechanism of acid excitation of the carotid gland to be a delicate adaptation of the regulation of the acid-base equilibrium in the organism and of the acid excitation itself as an information to the CNS on acidotic shifts in the blood.

The excitation of the carotid chemoreceptors and the pulmonary respiration in hypoxia has the following characteristics: On ablation of the carotid gland, by section of the sinus nerves or extirpation of the gland itself, the untrained organism in hypoxia is unable to respond by excitation of the pulmonary respiration. Further than that, after disconnection of the carotid gland, hypoxia causes a depression of the respiration, coupled with general depression of the animal.

A second characteristic feature of hypoxic excitation is that it occurs only after a considerable decrease in oxygen tension in the inspired air /144
(below 100 mm Hg), or at a corresponding drop in oxygen tension of the blood arriving at the carotid gland, and is not directly dependent on the degree of oxygen deficiency.

Finally, one of the essential characteristics of hypoxic excitation of the carotid chemoreceptors, in contrast to their acid excitation, is its pronounced inertia. Hypoxic excitation of the carotid gland occurs only after a certain latent period and is more protracted.

All this suggests that the hypoxic excitation of the carotid gland must be based on some other mechanism, inherent only to a certain chemoreceptor apparatus fundamentally differing from the apparatus responsible for the acid excitation of the carotid gland. It follows that hypoxic excitation of the carotid gland represents a specialized information of the CNS signaling a drop in blood oxygen level.

A comparison of the acid and hypoxic excitations of pulmonary respiration indicates their deep and basic difference. This difference obviously has a certain general biological meaning. It could be assumed that the chemoreceptor systems, developed in the course of evolution and present in various tissues where they react to variations in the acid-base equilibrium, are conditioned by the fact that this equilibrium which must have a definite level for normal function (for example, of the enzymatic systems) may differ in the various organs and tissues during their function, even if the organism has an environment /145 of constant oxygen content. These chemoreceptive systems are necessary to maintain a certain level of the acid-base equilibrium. One of these is the chemoreceptor system of the carotid gland, which is the first to react to even minute changes in the acid-base equilibrium of the blood under ordinary conditions of life of the organism and responds by excitation when the pH of the blood shifts toward the acid side.

The respiratory excitation in acute hypoxia results from a special mechanism which developed at a certain stage of evolution of the animal organism. This specialized system was fixed in the form of the chemoreceptor apparatus of the carotid gland, designed for selective reaction to any drop in the oxygen tension of the blood.

In conclusion, it should be noted that only few studies are available on the mechanism of changes in pulmonary ventilation taking place in acid and hypoxic excitation of the corresponding apparatus of the carotid gland. In particular, our knowledge on the mechanism of phase changes of the pulmonary ventilation (inspiration and expiration), of their depth and duration in acid and hypoxic excitation, is very scanty.

CONTRIBUTION TO THE QUESTION OF THE EFFECT OF HYPOXIA, INCREASING AT VARIOUS RATES, ON THE HUMAN ORGANISM

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This paper presents data on the effect of slowly increasing hypoxia on the human organism, as it applies to the loss of seal of the cabin of a flying vehicle.

In our experiments, we studied the work capability, motor coordination, and functional state of the higher nervous activity (EEG, conditioned-reflex activity, character of handwriting, skin-galvanic reaction), of the cardiovascular system (ECG, respiratory activity, blood filling and tonus of the blood vessels of the brain and extremities), respiratory system (rate and character of respiration, pulmonary ventilation, vital capacity, composition of alveolar blood, oxygen level of blood, etc.).

The studies established the dependence of the "altitude" tolerance of human subjects on the various regimes of decompression.

ELECTRIC ACTIVITY OF INSPIRATORY AND EXPIRATORY MUSCLES IN HUMAN SUBJECTS, IN HYPOXIA AND DURING STATIC MUSCULAR WORK

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M.Ye.Marshak and coworkers have reported that, in human subjects and in animals at rest, the inhalation of an oxygen-poor or CO_2-rich gas mixture, will lead to complex coordination problems of the electric activity of inspiratory and expiratory muscles (Marshak and Mayeva, 1961, 1961; Marshak, 1962; Kulik, 1962, 1963).

In hypoxia and in hypercapnia, the electric activity of the inspiratory muscles is intensified while that of the expiratory muscles is inhibited. On inhalation of pure oxygen, the electric activity of these muscle groups changes in the opposite direction, being intensified in the expiratory and inhibited in the inspiratory muscles.

In subjects untrained for static work, we often noted an increased electric activity of the inspiratory muscles, accompanied by depression or complete inhibition of the electric activity of the expiratory muscles. In most cases, this coincided with a disturbance of the respiratory rhythm and an impairment of the arterialization of the blood.

Immediately after stopping the static work, the electric activity of the expiratory muscles increased and that of the inspiratory muscles was inhibited.

The initial high level of electric activity of the inspiratory muscles in subjects untrained for static work declined markedly during training, while the electric activity of the expiratory muscles increased to a level above that at the beginning of training. /148

Our data on the variation in electric activity of the inspiratory and expiratory muscles during training for static muscular work reflect the dynamics of the functional state of the respiratory center.

DETERMINATION OF THE RELATIVE AND ABSOLUTE ERRORS IN CALCULATING THE PARAMETERS OF THE OXYGEN REGIME OF THE ORGANISM

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A considerable number of indices must be calculated in determining the parameters of the oxygen regime of the organism (N.V.Lauer and A.Z.Kolchinskaya). These calculations are based on experimental data obtained, under supervision by Dr. A.Z.Kolchinskaya, by staff members of the Institute of Physiology, UkrSSR Academy of Sciences, M.M.Seredenko, N.T.Khilinskaya, the present author, and others, during a study of the hypoxic states of the human organism. Experimental data necessarily are burdened with errors, due to the limited accuracy of the measuring instrument and to the time rate of change of the observed quantity itself. Thus, in the final calculation of the parameters, a certain error of unknown value will always be committed.

It is true that the second component of the error can be reduced by averaging a series of parallel or repeated observations, but the value of the first component cannot be diminished.

In this connection, it appears important to analyze the question of determining the limits of relative and absolute errors of each of the calculated parameters of oxygen utilization.

In interpreting the results, it must be borne in mind that the extreme error is hardly ever reached and that, in most cases (90 - 95%), the error will /150 not exceed two-thirds of its maximum (probable relative or absolute error).

In determining the absolute and relative errors for calculated quantities, we used the conventional formulas

$$|\Delta f| \leq \sum_{i=1}^{n} \left|\frac{\partial f}{\partial x_i}\right| |\Delta x_i| \tag{1}$$

$$|\delta f| \leq \sum_{i=1}^{n} \left|\frac{\partial}{\partial x_i} \ln f\right| |\Delta x_i| \tag{2}$$

where

$|\Delta f|$ is the value of the extreme absolute error,
$|\delta f|$ is the value of the extreme relative error, and

$$f = f(x_1, x_2, \ldots, x_n). \tag{3}$$

We assume that the absolute error in directly measuring the concentration

of a gas in air is 0.1% and will not exceed 0.3%, that the extreme absolute error in determining the minute volume of respiration fluctuates from 50 to 400 cm^3 (with a mode of 100 cm^3), that the respiratory rate is determined with an accuracy of 0.5 - 2 resp/min (with a mode of 1/min), that the barometric pressure is determined with an accuracy of 5 - 20 mm Hg and the temperature with an accuracy of $1^{\circ}C$.

Under these basic assumptions, we calculated the relative extreme errors of a number of different indices of the oxygen regime.

a) Errors of Measurement for Percent of Oxygen in Air

If it is assumed that the value of F_I varies in the range of 20.7 - 21.3%, then, at the extreme absolute error ΔF, the relative extreme error δf will be /151 (on the average)

ΔF absolute error	0.05%; 0.1%; 0.2%; 0.3%; 0.5%
δf relative error	0.24%; 0.47%; 0.93-0.96%; 1.41-1.45%; 2.35-2.41.

For a value of F_E fluctuating in the range of 16.5 - 17.6%, we similarly have

ΔF (absolute error)	0.05%; 0.1%; 0.2%; 0.3%; 0.5%
δf (relative error)	0.28-0.30%; 0.57-0.61%; 1.14-1.21%; 1.70-1.82%; 2.84-3.03.

Finally, for the values of F_A, varying in the range of 13.9 - 16.0%, we obtain

ΔF (absolute error)	0.05%; 0.1%; 0.2%; 0.3%; 0.5%
δf (relative error)	0.31-0.36%; 0.62-0.72%; 1.25-1.44%; 1.88-2.16%; 3.12-3.60%

All these errors are negligibly small, so that it can be assumed that the measurement of the % oxygen in the inspired, expired, and alveolar air has been performed with sufficient accuracy.

b) Errors of Measurement for Minute Volume

Considering that the minute volume (MV) may vary from 4000 cm^3 to 9800 cm^3 and that the extreme absolute error of its determination may range from 50 to 400 cm^3, the following Table can be compiled (see next page).

As will be clear from these calculations, the accuracy of measurement /153 below 300 cm^3 can already be considered impermissibly low, especially at low minute volume. However, this accuracy is composed of two components, one due to the error of observation (i.e., the absolute error), and the other due to the nonuniform respiration of the subjects. It can be shown that if there is a scattering of the values of R in three successive determinations of the MV, then the total absolute error of measurement of the true MV after n successive deter-

MV ΔV	50 cm^3	100 cm^3	200 cm^3	300 cm^3	400 cm^3
4000-4400	1.14 - 1.25%	2.27 - 2.50%	4.54 - 5.00%	6.82 - 7.50	9.09 - 10.0%
4600 - 5400	1.92 - 1.09%	1.85 - 2.17%	3.70 - 4.35%	5.56 - 6.52%	7.41 - 8.69%
5600 - 6400	0.78 - 0.89%	1.56 - 1.78%	3.12 - 3.57%	4.69 - 5.36%	6.25 - 7.14%
6600 - 7400	0.68 - 0.76%	1.35 - 1.51%	2.70 - 3.03%	4.05 - 4.55%	5.40 - 6.06%
7600 - 8400	0.59 - 0.66%	1.19 - 1.32%	2.38 - 2.63%	3.57 - 3.95%	4.76 - 5.26%
8600 - 9800	0.51 - 0.58%	1.02 - 1.16%	2.04 - 2.32%	3.06 - 3.49%	4.08 - 4.65%

minations (provided there is no systematic instrument error) will not exceed

$$\Delta \leq \frac{1.16R + \Delta V}{\sqrt{n}} \qquad (4)$$

Hence, it can be assumed that, if we prescribe the value of the error of measurement Δ and the scattering of R in the first three successive determinations, then - to keep the total error from exceeding 200 cm^3 - not less than the following must be measured,

Min:	200 cm	300 cm	400 cm	600 cm
50 cm^3	3 min	4 min	7 min	over 10 min
100 cm^3	3 min	5 min	8 min	over 10 min

It can be shown that the value of Δ is excessive in at least 5% of the cases.

The computational formula has been derived under the following assumptions:

a) In making n successive measurements, the extreme absolute mean-square error will be $2/\sigma/\sqrt{n}$.

b) To obtain an accuracy of Δ in calculating the mean of n observations with a probable error of not more than 5%, the following equality must be satisfied:

$$\Delta \leq \frac{t_{5\%}\,\sigma}{\sqrt{n}} \qquad (5)$$

c) To determine the value of σ from the scattering of three successive measurements, the quantity R must be divided by a factor taken from special Tables; in our case, this factor was 1.69.

c) Determination of Respiratory Rate

The practice of determining the respiratory rate per minute leads to an absolute error of the respiratory rate, being one respiration per minute (resp/min). However, this may be much too high. Starting from this and considering that the respiratory rate on the average is within 8 - 16/min, we obtain the following Table:

Δf	0.5	1.0	2.0	3.0	4.0
δf	3.12-6.25%	6.25-12.5%	12.50-25%	18.75-37.5%	25.0-50.0%

The above Table shows that the greatest absolute and relative errors take place in measuring the respiratory rate. The respiration must be checked over at least 1 min (assuming that the rate of respiration is strictly constant). If, however, even in the state of rest, the respiratory rate, taken over three successive minutes, varies by 2 - 3 resp/min, then to obtain the mean respiratory rate with an accuracy of 0.5 resp/min (i.e., with an accuracy to within one

complete respiratory cycle) the cycles would have to be counted for not less than 22 - 50 min, which would be impossible in practice. In this case, even a slight inaccuracy in determining the respiratory rate would introduce excessive errors into the values of the calculated indices. Therefore, wherever pos- /155
sible, a calculation per respiratory cycle should be avoided and replaced by a calculation per minute of respiration.

d) Calculation of the Physiological Dead Space

For Bohr's formula

$$V_D = \frac{F_E - F_A}{F_I - F_A} V_E \tag{6}$$

we find that

$$\Delta V_D = \frac{F_E - F_A}{(F_I - F_A)^2} \cdot [2 V_E \Delta F + (F_I - F_A) \Delta V_E] \tag{7}$$

$$\delta V_D = \delta |F_E - F_A| + \delta |F_I - F_A| + \delta V_E \tag{8}$$

In analogy to the above, it can be assumed that the minimum absolute extreme error at $F_E = 16.5 \pm 0.05\%$, $F_A = 13.9 \pm 0.05\%$, $F_I = 21.3 + 0.05\%$; $V_E = 250 \pm 11$ cm^3 will be 87.82 ± 5.05 cm^3, while the minimum extreme relative error is 5.75%. The maximum extreme absolute error, calculated under the assumption that $F_E = 17.6 + 0.2\%$, $F_A = 16.0 + 0.2\%$, $F_I = 20.7 \pm 0.2\%$ and $V_E = 1000 \pm 262.5$ cm^3 will be equal to $340.4 + 103.84$ cm^3, so that the maximum extreme relative error will be 30.86% (i.e., impermissibly high).

Finally, a calculation for the case of optimum (modal) values gives, for the initial values $F_E = 17.0 \pm 0.1\%$, $F_A = 15.0 + 0.1\%$, $F_I = 21.0 + 0.1\%$ and $V_E = 500 \pm 50$ cm^3, a value of the physiological dead space of 166.7 ± 19.4 cm^3 with an extreme relative error of 12.4%. /156

Obviously, the limits of accuracy of the value being determined are very wide; even an averaging over a considerable number of observations, which decreases the total absolute error by a factor of $\sqrt{n}$, will not yield the desired result, because of the low accuracy of measurement.

However, if the volume of the physiological dead space is not calculated per respiration but per minute of respiration, then - under the same assumptions (MV being 4000, 8000, and 6000 cm^3, respectively) - the resultant values of the dead space per minute will be 1405 ± 27 cm^3 with a minimum relative error of 2.5% and 2723 ± 184 cm^3 with a maximum extreme relative error of 7.11%, and, finally, 2000 ± 66.7 cm^3 with a mean relative error of 4.0%.

It is clear that this method of calculation reduces the relative extreme errors by a substantial amount. If we calculate the probable errors, a still greater decrease in the extreme relative errors as well as in the extreme absolute errors will result.

e) Calculation of Errors of Measurement of Alveolar Ventilation

Alveolar ventilation is determined approximately by the formula

$$\dot{V}_A = (V_E - V_D) f \tag{9}$$

The corresponding errors are determined as

$$\Delta \dot{V}_A = f(\Delta V_E + \Delta V_D) + (V_E - V_D)\Delta f \tag{10}$$

$$\delta \dot{V}_A = \delta f + \delta |V_E - V_D| \tag{11}$$

As indicated, in both cases the value of the respiratory rate and of V_D /157 enter into both formulas. Errors resulting from an inaccurate determination of the respiratory rate have a cumulative effect.

To decrease these errors, let us modify eq.(9), representing, in the form of a function, the initial data determined by direct measurements.

$$\dot{V}_A = \dot{V}_E \left[1 - \frac{F_E - F_A}{F_I - F_A} \right] \tag{12}$$

In this case, the formulas for determination of the errors take the form

$$\Delta \dot{V}_A = 2 \frac{F_E - F_A}{(F_I - F_A)^2} \Delta F + \Delta \dot{V}_E \frac{F_I - F_E}{F_I - F_A} \tag{13}$$

$$\delta \dot{V}_A = \delta \dot{V}_E + \delta (F_I - F_E) + \delta (F_I - F_A) \tag{14}$$

To obtain the maximum value of the relative extreme error, let us assign the following data: $\dot{V}_E = 8000 \pm 200$ cm^3, $F_I = 20.7 \pm 0.2\%$, $F_E = 16.5 \pm 0.2\%$, $F_A = 13.9 \pm 0.2\%$. The volume of alveolar air will be 5250 ± 303 cm^3, giving a relative extreme error of 6.11%.

For the initial indices $\dot{V}_E = 4000 + 50$ cm^3, $F_I = 21.3 \pm 0.05\%$; $F_E = 17.6 \pm$ $\pm 0.05\%$, $F_A = 16.0 \pm 0.05\%$, the volume of alveolar ventilation will be $\dot{V}_A =$ $= 2792.4 \pm 57.6$ cm^3, giving only a 2.1% relative extreme error.

Finally, for the optimum case, relative to the indices already discussed, the volume of alveolar air lies in the range of $4000 + 133.4$ cm^3, i.e., is determined with an extreme relative error of 3.4%.

The suitability of eq.(12) for practical use will be clear from the above.

f) Calculation of Errors in Determining the Reduction Factor /158

To reduce the amount of oxygen or other gas contained, under certain conditions, in a standard volume, i.e., the volume that would be occupied by it at 0°C under 760 mm Hg pressure, we determined the reduction factor by the formula

$$K = \frac{273}{760} \frac{B}{(273 + t°C)} \tag{21}$$

In this case, the computational formulas for the extreme errors take the form:

$$\Delta K = \frac{273}{760} \frac{[\Delta B (273 + t°) + B \Delta t°]}{(273 + t°)^2} \tag{22}$$

$$\delta K = \delta B + \delta t° \tag{23}$$

Since both barometric pressure and temperature are determined with a relatively high accuracy, the values of the extreme errors are small. Thus, in a pressure range of 450 - 760 mm Hg at 10 - 40°C, the extreme relative errors do not exceed the following values:

t°C \ B	450	500	550	600	650	700	750	760
10°	1.46%	1.35%	1.26%	1.18%	1.12%	1.06%	1.02%	1.01%
20°	1.45%	1.34%	1.25%	1.17%	1.11%	1.06%	1.01%	1.00%
30°	1.44%	1.33%	1.24%	1.16%	1.10%	1.05%	1.00%	0.99%
40°	1.43%	1.32%	1.23%	1.15%	1.09%	1.04%	0.99%	0.98%

It will be clear that, at an accuracy of pressure measurement within 5 mm Hg and an accuracy of temperature measurement within 1°C, the relative error will not exceed 1.5% of the value of the reduction factor over a rather wide range of measurements.

If the accuracy of measurement declines to half, i.e., to 10 mm Hg, then the error does not increase by more than 1%. /159

Knowing the error committed in determining the MV and also the value of the error introduced in determining the reduction factor, we can calculate the error committed in determining the reduced volume of any gas at any instant of the respiratory cycle.

g) Determination of Errors in Calculating the Reduced Volume of Inspired Air

We can determine the unreduced volume of the inspired air from a known MV, starting from equality of the volumes of inspired and expired nitrogen for 1 min. If we assume that the expired air is collected and analyzed for several minutes, and that its temperature, pressure, and humidity are equal to the temperature, pressure, and humidity of the inspired air, then the volume of the inspired air per minute can be determined from

$$\dot{V}_I = \frac{(100 - F^E_{CO_2} - F^E_{O_2})}{100 - F^I_{O_2}} \dot{V}_E \tag{24}$$

which leads to the following formulas for determining the extreme errors:

$$\Delta \dot{V}_I = \frac{\dot{V}_\varepsilon}{100 - F^{\mathcal{J}}_{O_2}} (\Delta F^{\varepsilon}_{O_2} + \Delta F^{\varepsilon}_{CO_2}) + \frac{100 - F^{\varepsilon}_{O_2} - F^{\varepsilon}_{CO_2}}{100 - F^{\mathcal{J}}_{O_2}} (\Delta \dot{V}_\varepsilon + \frac{\dot{V}_\varepsilon \Delta F^{\mathcal{J}}_{O_2}}{100 - F^{\mathcal{J}}_{O_2}}) \tag{25}$$

$$\delta \dot{V}_I = \frac{(\Delta F^{\varepsilon}_{O_2} + \Delta F^{\varepsilon}_{CO_2})}{100 - F^{\varepsilon}_{O_2} - F^{\varepsilon}_{CO_2}} + \delta \dot{V}_\varepsilon + \frac{\Delta F^{\mathcal{J}}_{O_2}}{100 - F^{I}_{O_2}} \tag{26}$$

Let the accuracy of the MV determination be 100 cm^3, and let the MV be determined from several one-minute measurements without substantial scatter [in the opposite case, as follows from Section (b), the errors would be considerably higher].

Furthermore, let the accuracy of measurement of the gas concentration in the air be 0.1%. Then, making use of the fact that the oxygen concentration in the inspired air is almost constant, we can find the extreme relative error /160 for various MV, provided that the nitrogen concentration in the inspired air fluctuates in the range of 79.0 - 81.5%.

$\dot{V}_\varepsilon$:	4.0 -4.4 ltr	4.6-5.4ltr	5.6-6.4ltr	6.6-7.4ltr	7.6-8.4ltr	8.6-9.8ltr
$\delta \dot{V}_I$:	2.6-2.9%	2.2-2.5%	1.9-2.2%	1.7-1.9%	1.6-1.7%	1.4-1.5%

We can then determine the error committed in determining the reduced volume of inspired air. As we have seen, the error obtained on application of a correction for the difference in the composition of inspired and expired air is small, not exceeding 0.5%. The correction for the error in determining the reduction factor, as has been shown, does not exceed 1 - 1.5%. The total extreme relative error, for a given accuracy of determination of the MV, will not exceed 4%. However, as already noted, a decrease in the accuracy of determination of the MV will result in a considerable increase of the extreme relative error. Thus, at an accuracy of measurement of the MV to 200 cm^3, the extreme relative error is increased at various MV to 1 - 2.5% and may reach 6.5%.

h) Determination of the Error of Calculating the Oxygen Consumption by Body Tissues

Neglecting, as before, the variations in relative humidity of the inspired air by comparison with that of the expired air, we can determine the oxygen consumption of the organism per minute by the formula

$$\dot{V}^{Reg}_t = k(\dot{V}_I F^{I}_{O_2} - \dot{V}_\varepsilon F^{\varepsilon}_{O_2}) \tag{27}$$

where k is the reduction factor.

It follows from this expression that

$$\Delta \dot{V}^{Reg}_t = \Delta k(\dot{V}_I F^{I}_{O_2} - \dot{V}_\varepsilon F^{\varepsilon}_{O_2}) + k(F^{I}_{O_2} \Delta \dot{V}_\mathcal{J} + F^{\varepsilon}_{O_2} \Delta \dot{V}_\varepsilon + \dot{V}_I \Delta F^{I}_{O_2} + \dot{V}_\varepsilon F^{\varepsilon}_{O_2}) \tag{28}$$

$$\delta \dot{V}_t^{Reg} = \delta K + \frac{(\dot{V}_I + \dot{V}_E)\Delta F_{O_2} + F_{O_2}^I \Delta \dot{V}_I + F_{O_2}^E \Delta V_E}{\dot{V}_I F_{O_2}^I - \dot{V}_E F_{O_2}^E} . \quad (29)$$

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This equation is highly complicated for actual calculation, so that it is preferable to calculate the relative extreme error in this case by a graphical method. However, we can make use of the fact that the volumes of the inspired and expired air differ by a small quantity. Assuming them as equal, eq.(29) can be represented in the following form:

$$\delta \dot{V}_t^{Reg} = \delta K + \delta \dot{V}_E + \frac{\Delta F_{O_2}^I + \Delta F_{O_2}^E}{F_{O_2}^I - F_{O_2}^E} . \quad (30)$$

Here the first two terms are known, and the volume of the third is given in the following tabulation

$F_{O_2}^I - F_{O_2}^E$	3.3%	3.6%	3.9%	4.2%	4.5%	4.8%	5.2%
$\delta(F_{O_2}^I - F_{O_2}^E)$	6.06%	5.56%	5.12%	4.76%	4.44%	4.16%	3.84%

Knowing that the relative error of the reduction factor lies in the range of 1 - 1.5% while the relative error of the MV, at an accuracy of measurement to 100 cm^3, is from 1 to 2.5%, we reach the conclusion that the total relative error in the determination of the amount of oxygen taken up by the tissues is not less than 6 - 10.6%. Under more rigorous assumptions, determining $\dot{V}_I$ in terms of $\dot{V}_E$, we obtain an additional increase of 0.5% in the extreme relative error. As indicated by these calculations, the maximum error in the determination of oxygen consumption by the tissues results from the inaccuracy in determining the oxygen concentration in the air, an inaccuracy which is difficult to eliminate.

i) Determination of the Minute Volume by Fick's Formula

The Fick formula is considered the most accurate method of determining the MV:

$$\dot{Q} = \frac{\dot{V}_t^{Reg}}{F_a - F_v} \cdot 100 \quad (31)$$

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where

F_a is the concentration of oxygen in the arterial blood, and

F_v is the concentration of oxygen in the venous blood.

Expressing this formula in terms of directly measured quantities, it can be written as follows:

$$\dot{Q} = K\dot{V}_E \frac{F_{N_2}^E F_{O_2}^I - F_{N_2}^I F_{O_2}^E}{F_{N_2}^I (F_a - F_v)} = \frac{K\dot{V}_E}{F_a - F_v}\left[\frac{100(F_{O_2}^I - F_{O_2}^E) - F_{CO_2}^E F_{O_2}^I}{100 - F_{O_2}^I}\right]$$

and the absolute and relative extreme errors produced by its use will be

$$\Delta\dot{Q} = \frac{\Delta K}{K}\dot{Q} + \frac{\Delta\dot{V}_E}{\dot{V}_E}\dot{Q} + \frac{\Delta F_a + \Delta F_v}{F_a - F_v}\dot{Q} + K\frac{\dot{V}_E}{F_a - F_v}\left\{\frac{1}{100 - F^J_{O_2}}\left[100(\Delta F^I_{O_2} + \Delta F^E_{O_2}) + \right.\right.$$
$$\left.\left. + \Delta F^E_{CO_2} F^I_{O_2} + \Delta F^J_{O_2}\Delta F^E_{CO_2} + \frac{\Delta F^J_{O_2}}{100 - F^J_{O_2}}\right]\right\}; \quad (32)$$

$$\delta\dot{Q} = \delta K + \delta\dot{V}_E + \delta(F_a - F_v) + \frac{100\Delta F + (F^I_{O_2} + F^E_{CO_2})\Delta F + \frac{\Delta F}{100 - F^J_{O_2}}}{100(F^J_{O_2} - F^E_{O_2}) - F^E_{CO_2} F^I_{O_2}}; \quad (33)$$

A direct application of these formulas is still more difficult than that of the preceding formulas; because of this, we will confine the calculation to the construction of nomograms for determining the extreme relative error when working with Fick's formula in each specific case. In so doing, we assumed that F_a varies by 10 - 21% and F_v by 5 - 16%, and that the accuracy of determination of these two concentrations is not less than 0.3%.

For a rough estimate of the error in the determination of the MV, eq.(30), derived above, can be used.

Then, eq.(33) can be approximated by eq.(34):

$$\delta\dot{Q} \approx \delta\dot{V}_t^{P_{A_2}} \cdot \delta(F_a - F_v) \quad (34)$$

The relative percentage error $\delta(F_a - F_v)$ is given for various values of $F_a - F_v$ in the following tabulation:

$F_a - F_v$:	1%	2%	3%	4%	5%	6%	7%	8%
$\delta(F_a - F_v)$:	60.0%	30.0%	20.0%	15.0%	12.0%	10.0%	8.6%	7.5%
$F_a - F_v$:	9%	10%	11%	12%	13%	14%	15%	16%
$\delta(F_a - F_v)$:	6.7%	6.0%	5.45%	5.0%	4.62%	4.29%	4.00%	3.75%

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As already shown, the quantity $\delta\dot{V}_t^P$ can be given in the form

$$\delta\dot{V}_t^{P_{A_2}} = \delta K + \delta\dot{V}_E + \delta(F^I_{O_2} - F^E_{O_2})$$

where the quantity $\delta(F^I_{O_2} - F^E_{O_2})$ varies from 3.84 to 6.67%; the quantity $\delta\dot{V}_E$ varies from 1 to 2.5% and the quantity δk, from 1 to 1.5%.

Hence, it is obvious that the total extreme relative error of determination of the MV by Fick's formula cannot be less than 9.6%, although it may considerably exceed this value. As we have seen, the main portion of the errors committed in using Fick's formula is not so much due to the errors in determining the oxygen consumption per minute as to the errors in determining its concentration in the blood.

j) Determining the Minute Volume by Starr's Formula

If the MV is determined by the empirical Starr formula

$$\dot{Q} = PR(101 + 0.50\ PP - 0.59\ DP - 0.61\ A) \quad (35)$$

where PR is the pulse rate, PP the pulse pressure, SP the systolic pressure,

DP the diastolic pressure, and A the age in years, then certain computational errors will also be committed here. Assuming that the PR is determined with an error of 2 beats/min, that the SP is measured with an error of 5 - 10 mm Hg, DP with an error of 10 - 20 mm Hg, and A with an error of rounding to the nearest year, the following expression will be obtained for the extreme absolute and relative errors of calculation (disregarding, for the time being, the accuracy of the Starr formula):

$$\Delta\dot{Q} = \Delta PR \cdot CO + PR\,(0.50\,\Delta SP + 1.09\,DP + 0.61\,\Delta A) \qquad (36)$$

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$$\delta\dot{Q} = \delta PR + \frac{0.50\,\Delta SP + 1.09\,DP + 0.61\,\Delta A}{101 + 0.50\,SP - 1.09\,DP - 0.61\,A} \qquad (37)$$

Since eq.(37) depends on three valuables, the determination of the extreme relative error by the tabular method is somewhat tedious. Therefore, we will here confine ourselves to considering only the extreme cases.

At values of SP = 130 ± 5; DP = 100 ± 15; A = 85 ± 1, the value of $\delta\dot{Q}$ at PR = 40 ± 2 is 276%.

At SP = 140 ± 5; DP = 80 ± 10; A = 20 ± 1; and PR = 180 ± 2, the value of $\delta\dot{Q}$ does not exceed 12.2%.

Finally, at the optimum values SP = 120 ± 5; DP = 80 ± 10; A = 30 ± 1; and PR = 80 ± 2, the value of $\delta\dot{Q}$ is 28%.

As shown, a calculation by the Starr formula leads to greater relative errors than by the Fick formula. The possibility for decreasing these errors lies mainly in substantially increasing the accuracy of measurement of DP in the range of 80 - 100 mm Hg. Averaging a series of successive measurements of the DP might be useful here. Thus, as indicated above, even averaging the results of three successive measurements may increase the accuracy of measurement by a factor of 1.7, thus considerably decreasing the main component of the relative extreme error, produced by the accuracy of measurement of DP.

Next, using these formulas as basis, we determine the possible errors in calculating all stages of the oxygen cascade of the organism. The only exception will be the determination of errors in finding the partial oxygen pressure in the arterial and venous blood, since this depends on the form of the hemoglobin dissociation curve and is easier to determine, for various concentrations, by a graphical method.

Summarizing our study, let us isolate some of the most important components exerting an influence on the increase of the extreme relative errors of calcu- /165
lation.

As shown above, the primary cause for the increase in the extreme relative errors of calculation is not the inadequate accuracy of the apparatus but the dispersion of the results of successive determinations. By virtue of this fact, the requirements are considerably increased for determination of the stationary oxygen regime of the organism during the time of investigation, which in turn

demands averaging of the data obtained over several successive time intervals.

Our second conclusion is that the calculation of the oxygen regime for a single respiratory cycle is subject to considerably greater errors than the calculation for 1 minute of respiration, and that therefore the latter should be used wherever possible.

Finally, an important conclusion is the fact that, in determining the difference between two gases of closely adjacent concentrations, the magnitude of the extreme relative error increases sharply. This makes it desirable to measure the oxygen concentration of the arterial and venous blood with a higher degree of accuracy, which can be accomplished by running a series of parallel determinations and averaging the resultant data.

The same statement applies to determining the pulse pressure when the Starr formula is used in measuring the minute volume.

THE OXYGEN REGIME OF THE ORGANISM /166

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As a result of the evolution of the organic world in a medium with a certain oxygen content, oxidation has been the most important source of energy for physiological processes. It has been the struggle for oxygen that has largely shaped the course of evolution of mammals and man, the development of the complex system of specialized organs and mechanisms serving the oxygen metabolism. This same struggle has been responsible for the development of the respiratory organs, the circulatory system, the erythron, and many other mechanisms whose function is to supply the cells with oxygen.

Thus, as a result of evolution, the oxygen metabolism has been defined as a complex but still unitary process requiring numerous physiological, biochemical, physical and other mechanisms for its accomplishment, mechanisms which, with amazing accuracy, ensure constancy of the oxygen parameters - under normal conditions - at each stage of oxygen metabolism in the organism.

The high degree of organization and coordination of the oxygen metabolism, the interdependence of its parameters over the entire path of oxygen in the organism, the interdependence and to some extent the interchangeability of the activity of the regulatory organs and systems, has not yet been fully appreciated by physiologists in their considerations of the oxygen metabolism.

Despite the wealth of data on the physiology of respiration and on other systems that control the supply of oxygen to the lungs, to the blood, and to /167 the tissues, as well as its utilization in the cells, the approach to the study of the oxygen metabolism as a complex process integrating the activity of many regulating mechanisms, has not been properly defined.

It must be emphasized that the classical physiology of respiration, which considers oxidation as the essence of respiration, assumed it to be self-evident that oxidation was in constant coordination with the other manifestations of life. Haldane, in studying the regulation of respiration, emphasized its subordination to the physiological needs of the organism, to the organism's demand for oxygen, and to its necessity of eliminating carbon dioxide.

Subsequently, excessive specialization resulted in the study of many functions separately from other forms of activity of the organism, and the facts on their regulation were not properly correlated with the physiological needs of the organism.

To a considerable degree, this can also be explained by the fact that although organic physiology has accumulated much valuable information on the functions of the individual organs and physiological systems and on their neurohumoral regulation, it has nevertheless been dominated by anatomical concepts

and thus neglected the study of physiological processes with reference to their successive quantitative characterization at various stages in the organism.

Although I.M.Sechenov, Krog, Bohr, Haldane, Barcroft, van Slyke, Warburg, and other classical physiologists in the area of respiration and other fields /168 developed methods and formulas that are still in use today for calculating and determining the oxygen parameters, and although these authors paid special attention to the quantitative aspects of the problem, no consistent quantitative characterization of oxygen metabolism as such has ever been published.

A definite step forward in the evaluation of the oxygen metabolism as a whole was taken by A.M.Charniy (1947) who proposed the term "oxygen budget of the organism". Aside from the methodological difficulties involved in the formulation of the concept of an oxygen budget of the organism (as he himself pointed out), the basic idea of "oxygen budget of the organism", while giving an overall quantitative evaluation of the oxygen metabolism, did not yield a consecutive characterization of various stages of the oxygen metabolism and did not elucidate the mechanisms of its regulation.

The general technical advance in the theory of control and the development of laboratory techniques during the past 10 - 15 years, in connecting with the widespread use of electronics in physiology, the appearance of oxyhemometry, polarography, etc., the possibility of more accurate and more rapid determination of the oxygen parameters in dynamics, at simultaneous registration of the indices of activity of the various physiological systems participating in oxygen metabolism, and the adoption of a different approach to the problem of oxygen metabolism, all led to a number of investigations which permitted, to a greater or lesser degree, a characterization of the processes as a whole and the introduction of new concepts of definition.

Thus, the recent American literature has proposed terms such as "overall oxygen gradient" and oxygen "cascade", reflecting the gradual decrease of the partial oxygen pressure along its path in the organism (Luft, Armstrong, /169 1962; Hurtado, 1963). This index has been compared with the minute volume, the alveolar ventilation, the rate of O_2 diffusion, the oxygen capacity of the blood, the dissociation curve of oxyhemoglobin and CO_2, etc. (Fenn, Rahn, 1959; Hurtado, 1963).

The concept of the overall oxygen "gradient" (the gradient between the pO_2 of the inspired air and the pO_2 of the mixed venous blood) within which the authors distinguish the atmosphero-tracheal, the tracheo-alveolar, the alveolo-arterial, and the arteriovenous gradients of pO_2 which is one of the integrating indices of oxygen metabolism, creates the idea of physical conditions under which oxygen exchange proceeds at various stages of the oxygen cascade, yielding data on the economy of the efforts of the organism under changed conditions (for example, during the process of acclimatization to high mountain climates; Hurtado).

However, the gradients of partial oxygen pressure cannot completely characterize the changes in the oxygen metabolism, since they do not reveal the relation between tissue oxygen demand and oxygen reserves at various stages of the metabolism and since they do not give a quantitative characterization of the

oxygen metabolism.

Owing to the fact that the cascade of changes in pO_2 gives an idea of the conditions under which oxygen exchange takes place rather than of the oxygen exchange itself, we believe that the introduction of quantitative characteristics of oxygen exchange is of exceptional importance. We mean here oxygen /170 parameters that successively reflect the amount of oxygen arriving in unit time from the inspired air (q_IO_2), delivered to the alveoli (q_AO_2), transported by the arterial blood to the tissues (q_aO_2), carried away by the venous blood from the tissues (q_vO_2), and consumed by the tissues themselves (q_tO_2).

A graphic representation of these parameters, represented in the form of a cascade of qO_2, yields a series of quantitative characteristics of oxygen exchange in the organism, which will be discussed below.

A comparison of the cascades of qO_2 and pO_2 clearly shows that, at various stages of the metabolism, these basic oxygen parameters are interdependent to some extent.

The dependence of the values of the parameters on the various stages of the cascades, the fact that they are sensitively controlled by the physiological systems in accordance with the oxygen demand of the tissues, predetermined by phylogenesis and ontogenesis for the various vital events, define the oxygen metabolism as a process taking place in a certain regime or set of operating conditions, i.e., permit us to speak of an "oxygen regime" of the organism and to assert that this regime is maintained by the regulatory system of the oxygen regime (RSOR).

The oxygen regime of the organism can be defined as the set of interrelated oxygen parameters (pO_2 and qO_2) of the inspired and alveolar air, of the arterial and venous blood, and of the tissues, determined by the functional indices of the external respiration, the blood circulation, the erythron, the physicochemical and biochemical processes directed toward maintenance of a proper match between the oxygen demand of the tissues and supply of oxygen to there.

Since the most important changes in the oxygen parameters take place in the pulmonary reservoir, in the blood washing the alveoli, and in the blood washing the tissues, we believe it possible to distinguish these points as elements or stages of the object controlled by the RSOR. /171

In the pulmonary reservoir, the inspired air undergoes a considerable change in composition. Depending on the pulmonary ventilation, i.e., as a function of the minute volume; the frequency and depth of respiration (which, in turn, depend on the pCO_2 of the alveolar air and the arterial blood); the ratio of the respiratory volumes; the degree of alveolar ventilation; the quantity of oxygen transported by the blood in unit time; the degree of oxygen deficiency in the venous blood; the diffusional power of oxygen across the alveolo-capillary membrane, etc., the oxygen parameters of the inspired air are transformed into the amount of oxygen ventilated in unit time in the alveoli, and the partial oxygen pressure of the alveolar air.

In the blood supplying the alveoli, interaction takes place between the

oxygen parameters of the alveolar air and of the venous blood, which is not only determined by the values of these parameters, but also by such factors as uniformity of alveolar ventilation; ratio of alveolar ventilation to blood flow through the capillaries of the lungs; existence of arteriovenous shunts in the lungs; oxygen capacity of the blood; affinity of hemoglobin for oxygen (depending to a certain extent on the CO_2 content of the blood and the pH of the blood); rate of diffusion of oxygen across the alveolo-capillary membranes, etc. As a result of this interaction, the oxygen parameters of the alveolar air and of the venous blood are converted into the parameters of the arterial blood, which are the oxygen tension and the amount of oxygen transported by the arterial blood in unit time.

In the blood supplying the tissues, the influence of oxygen consumption by the tissues, depending on the rate of blood flow, of capillary irrigation /172 and filling, on the rate of diffusion of oxygen across the capillary-tissue membranes and the tissue fluids, on the properties of the tissue globins and enzymatic systems, etc., the oxygen parameters of the arterial blood are converted into the amount of oxygen transported by the venous blood to the lungs and the partial oxygen pressure of the venous blood.

In the tissues, which are the oxygen consumers and thus constitute the load on the system, the utilization of oxygen proceeds as a function of the oxygen parameters of the arterial and venous blood, of the state of the tissue and its neurohumoral regulation, and of the processes taking place on the tissue, cellular, and molecular levels.

The differentiation of the above elements of the RSOR is largely arbitrary, since the changes in oxygen parameters take place over the entire path of oxygen in the organism, not only at the above points. Such variations also occur in the upper respiratory tract, in the pulmonary venules and arterial bloodvessels, as well as in the arterioles, venules, and veins of the systemic circulation. However, by comparison with the transformation of the oxygen parameters in the above-mentioned elements of the RSOR, these changes are not extensive and are far less significant for the oxygen metabolism as a whole.

The quantitative accounting of the oxygen and its partial pressure in the various elements of the oxygen regime and the graphic representation of these oxygen parameters in the form of cascades, permits (as stated above) the introduction of additional criteria for evaluating the oxygen regime. These criteria can be divided into three groups.

The first group of indices, permitting an evaluation of the oxygen regime from the variation in the amount of oxygen, can characterize this regime by /173 level, intensity, and effectiveness.

The second group of indices, evaluating the pO_2 level and the pO_2 gradients in the various elements of the RSOR, can characterize the intensity of the oxygen regime.

The third group of indices, characterizing the interrelations between the regulatory influences of the functional systems and the oxygen consumption of the organism, permits an evaluation of the economy of the oxygen regime.

The overall level of the cascade qO_2 is determined by the amount of oxygen in the following steps of this cascade: 1) inspired air; 2) alveolar air; 3) arterial blood; 4) venous blood. The level of the cascade qO_2 is naturally not identical with the concept, generally accepted in physiology, of the level of oxygen metabolism, which characterizes only the oxygen consumption of the tissues, i.e., the stress on the system*.

The intensity of the oxygen regime is defined by the amounts of oxygen in each step of the cascade, related to the weight or surface of the body.

The efficiency of the oxygen regime is characterized by the ratio of the amount of oxygen at the input of each element to the amount of oxygen consumed and to the interrelations between these quantities.

The stress of the oxygen regime is characterized by indices such as the level of pO_2 in the various steps of the cascade and the pO_2 gradients between them. Significant for the determination of the stress of the oxygen regime /174 in the second and third steps are those portions of the oxyhemoglobin dissociation curve to which the arteriovenous gradient of pO_2 corresponds.

The economy of the oxygen regime may be judged from many indices determining the relation of the parameters of activity of the physiological systems that participate in the regulation of the oxygen regime.

Thus, one can judge the economy of the oxygen regime (OR) in the first stage from the ventilation equivalent, the oxygen utilization factor, the oxygen effect of the respiratory cycle, the ratio of respiratory volume, the oxygen value of pulmonary ventilation, etc.

In the second and third stage, the economy of the oxygen regime may be characterized by the relation between minute volume and oxygen consumption, by the oxygen effect of a cardiac contraction (oxygen consumption), and by the systolic index. The necessity of the above approach to the oxygen metabolism arose during an analysis of the voluminous experimental material obtained in studies of the hypoxic states of human subjects (A.Z.Kolchinskaya, 1958, 1959, 1961, 1964, 1965; V.V.Turanov, 1958, 1961; M.M.Seredenko, 1964, 1965; N.T. Khilinskaya, 1965) and of animals (N.V.Lauer, 1951, 1959, 1960, 1961, 1963, 1964, 1965; N.V.Lauer and Kolchinskaya, 1958, 1959, 1960, 1961, 1962, 1963, 1964, 1965; M.M.Koganovskaya, 1962, 1963, 1964; M.M.Seredenko, 1962, 1963, 1964; V.V.Turanov, 1963, 1964; Yu.V.Semenov, 1960, 1961, 1963, 1964).

This analysis showed that the oxygen regimes of the organism at the various stages of individual life are distinguished by a number of features, common /175 to a given age group.

First of all, there are differences between age groups in the general level of the cascade qO_2. In a middle-aged subject, with greater body weight and body surface than in youth or childhood, the amount of oxygen furnished by pulmonary

* See the article by A.Z.Kolchinskaya, N.V.Lauer, and Ye.A.Shkabara "Regulation of the Oxygen Regime of the Organism" in this book.

alveolar ventilation and the amount of oxygen transported by the arterial and venous blood, are also greater.

It is a striking fact that the cascade qO_2 of a young subject differs from that of other ages by a certain irregularity of the steps, which is most clearly manifested at the levels of alveolo-arterial blood.

It is generally known that the amount of oxygen transported by the arterial blood in unit time is directly proportional to the minute volume (MV) and to the concentration of oxygen in the arterial blood. The MV at the age of puberty lags considerably (throughout the organism) behind the cardiac output of the adult, which is reflected in the reduced amount of oxygen delivered in unit time by the arterial blood to the tissues of the young subject.

The amount of oxygen ventilated in the lungs and alveoli and carried from the lungs by the arterial blood, like the oxygen consumption per kg of body weight, are high in children (5 - 6 years of age), are lower at puberty than in childhood but still remain somewhat higher than in middle age, i.e., the intensity of the oxygen regime in a young subject is higher than in middle age and old age.

The overall gradient of the cascade, qO_2, may be of a certain value in /176
evaluating the oxygen regime. The oxygen regime in youth may serve as an example.

The efficiency of the oxygen regime may be somewhat enhanced in the compensable stages of hypoxia, owing to the fact that an oxygen consumption equal to, or somewhat higher than, the initial level may be satisfied by decreased amounts of oxygen at the input and output of the stages of the RSOR; this is particularly distinct in middle age, which is distinguished by the highest degree of perfection in the regulation of the oxygen regime.

Also of interest are the ratios of the amounts of oxygen at each stage of the cascade to the consumption of oxygen on that stage, which may be used to characterize the efficiency of the OR in its several stages. For instance, considering that the oxygen intake in the lungs and alveoli in middle age is, respectively, four and three times as much as the consumption, while in youth it is six and five times as much, the impression is gained that the OR is more efficient in the first and second stages in middle age than in youth. Owing to the high specific MV (per kg), which ensures a high qO_2 in the arterial blood despite the apparently greater oxygen consumption, the efficiency in the third stage of the OR in youth is also lower than in middle age. In childhood and in youth, the important role played by hemodynamics ensuring physiological reliability of oxygen supply to the tissues, is particularly distinct.

According to Yu.V.Semenov and the literature, the relatively low oxygen capacity of the blood observed in puppies in early age during the period of /177
sexual maturation (19.5 vol.%), still does not reach its level in grown dogs (22.9 vol.%). This relatively low oxygen capacity is due primarily to the low hemoglobin concentration and erythrocyte count per mm^3 (ery. = 6600 ± 640 in dogs of medium age; 4530 ± 330 in 3 month old puppies and 5600 ± 380 in 6 - 7

month old puppies).

At the same time, the total number of erythrocytes circulating in the blood (per kilogram of body weight, related to the volume of circulating blood) remains relatively low in early age. In grown dogs it was 37 ± 7 mℓ/kg, in 1.5 month old puppies it was 27 ± 4 mℓ/kg, and in puppies at pubertal age, it was 30 ± 4 mℓ/kg; however, when the time factor is introduced, the opposite tendency is disclosed: The number of erythrocytes transported by the blood per minute and per kilogram of body weight is greater at an early age than at medium age, as is also true for the amount of oxygen delivered to the tissues of the arterial blood in the same unit time.

The number of erythrocytes carried by the blood per minute, in dogs of various ages under normal conditions, is as follows: in dogs of middle age, 647×10^9; in 2 - 3 week old puppies, 777×10^9; in 6 - 7 month old puppies, 957×10^9. It is a striking fact that also the oxygen value of the erythrocytes is greater in early age than in the mature animal.

Under conditions of hypoxia, with declining pO_2 in the inspired air, the intensified circulation can deliver more oxygen to the tissues than the quantity ventilated in the alveoli during the same time. However, this is observed /178 in grown animals only in cases of marked oxygen insufficiency, while in puppies of pubertal age it is also observed at less marked hypoxia.

As already noted, a comparison of the activity indices of the functional systems, participating in the supply of oxygen to the tissues, with the oxygen consumption is able to characterize the economy of the oxygen regime as a whole and of its individual stages, and also yields information on the role of each function in the regulation of the OR. Judging from the distribution of the respiratory volumes, the indices of the ventilation and hemodynamics equivalents, the oxygen efficiency of the respiratory and cardiac cycles, etc., it seems that the oxygen regimes at the various periods of individual development are distinguished by different degrees of economy, i.e., that the participation of the various functions in the supply of oxygen to the tissues during the various stages of growth, is unequal. There is reason to believe that the OR is most economical in middle age, while in early age, youth and old age, it is less economical.

This low economy of the OR in youth and old age is already manifested in the first stage of the RSOR. For example, in an adult, each 100 mℓ of oxygen consumed is extracted from 2.5 ltr of air ventilated in the lungs; the child requires 3 ltr, while an old person must pass about 3.2 ltr of air through the lungs to ensure the same result.

The same relationship exists with respect to the oxygen consumed in one respiratory cycle, during which the adult uses 20 mℓ of oxygen, the child 5 mℓ, the young person 10.5 mℓ and the old person 12 mℓ.

The hemodynamic expenditures correspond to this lower economy at this age. It is sufficient to state that each 100 mℓ of oxygen used by the tissues is /179 extracted by the child or old person from about 1700 mℓ of arterial blood, by the youth from 1470 mℓ, and by the middle-aged person from 1430 mℓ; or that the

oxygen efficiency of one cardiac cycle, i.e., the amount of oxygen taken up by the tissues during a single cardiac cycle, is 1.2l in the 5 - 6 year old child, 2.6 in the youth, and 4 ml of O_2 in the middle-aged person. Satisfaction of the physiological oxygen requirements of the child, young person, or old person places a greater strain on the hemodynamics than in the middle-aged person.

The pO_2, the overall oxygen gradient, and the gradient at the input and output of the various units of the RSOR, are of great importance for characterizing the OR; for the gradient between the third and fourth units (i.e., for the arteriovenous gradient of pO_2), the position at which it is located on the oxyhemoglobin dissociation curve may well characterize the stress on the OR.

In children, the high level of pO_2 of the arterial blood results in a high gradient between the third and fourth units of the OR and its high position on the oxyhemoglobin dissociation curve. In old age, in contrast, the lowest value of the gradient $P_{A-B}O_2$ falls on the lowest and steepest segments of the curve, i.e., in childhood the conditions are more favorable for extraction of oxygen from the alveoli by the blood, and from blood by the tissues, and the OR is less stressed.

The cascade of pO_2 in youth is distinguished by a higher alveolo-arterial and a lower arteriovenous gradient, the arteriovenous gradient in youth being /180 located on a lower segment of the oxyhemoglobin dissociation curve than in children; therefore, the pO_2 of the blood of the tissue capillaries is lower, while the entire oxygen regime during the period of puberty is more stressed than in childhood.

The stress of the OR increases under conditions where the mismatch between the assigned and current values of the partial pressure of oxygen in the various units of the OR is increasing, as, for example, may take place with declining pO_2 in the inspired air.

It must be emphasized that the proposed characteristics of the OR are not entirely identical with the characteristics generally adopted for the oxygen metabolism.

The approach to the oxygen metabolism as a unitary process, which can be evaluated as a definite regime characterized by its specific features, makes it possible to introduce objective quantitative evaluations of the OR as a whole and of its components, so as to determine the oxygen value of the reorganizations of the functional systems (external respiration, hemodynamics, erythron), and will facilitate the introduction of mathematical analysis and of mathematical and technical simulation.

The proposed approach also reveals the aspects of control which have not yet found proper recognition. It is difficult to believe that so complex a physiological process as the supply and exchange of oxygen, with its exceptionally important significance for life, could be accomplished in vital situations /181 of widely differing patterns merely by nervous control over the various functional systems; at least there should be an automatic control by the oxygen parameters in a single unitary system of oxygen regime control, providing greater biological reliability as well as greater economy of functions.

PROBLEMS OF HYPOXIA IN SPORTS MEDICINE /182

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The literature devoted to the problem of hypoxia is extensive and deals with its most varied aspects, clinical, morphological, biochemical, physiological, psychological, etc. The monographs by Z.I.Barbashova and A.Z.Kolchinskaya have recently made a valuable contribution to the study of this problem, which is true also of the large and brilliant group of authors participating in the Symposium "Oxygen Insufficiency" (1963), A.F.Makarenko, N.N.Sirotinina, Ye.V. Kolpakova, N.V.Lauer, M.I.Gurevich and A.Z.Kolchinskaya, editors.

The most extensive field of research covered the problems of hypoxia at various altitudes and in high mountains. The problems of adaptation to hypoxia have been extensively studied in the altitude chamber, which has substantially broadened our idea of the processes of adaptation to hypoxia. To a certain extent, the data of these studies have assisted in understanding the features of activity of the body in high-altitude flights and mountain climbing.

In recent years, the problems of hypoxia in the physiology and medicine of athletics have been more widely studied. This is particularly shown by the recent conference at Alma-Ata, from March 8 to 13, 1965, on the acclimatization of athletes in a mountain locality and the symposium on hypoxia in muscular /183 activity. Most of the studies were concerned with the individual tolerance of hypoxia by healthy trained persons under mountain conditions, or with special function tests (holding of breath, breathing tests in a closed space up to the limit of individual tolerance, etc.). The systematic studies by Professor A.B. Gandel'sman and coworkers, extending over many years, show that athletes not only develop high resistance to hypoxia but also improve their interoceptive sensitivity to acute hypoxemia and hypercapnia. The athletes become able to analyze in detail the changes taking place in the inner medium of the organism (drop in oxygenation level of the blood) after only a single "sensing" of the acute hyperoxemic and hypercapnic shifts in respiration in an enclosed space.

Relatively few studies have been devoted to the features of respiratory activity during muscular hypoxia and its influence on the adaptation processes of the organism and of its individual systems and organs.

Effective methods of increasing the resistance of the body to the combined effect of muscular stress and reduced atmospheric pressure have been investigated under laboratory conditions by Professor N.V.Zimkin and coworkers. Professor V.S.Farfel' and associates are extending their study of the resources of the respiratory system under hypoxia. Original research is being performed by the Department of Physiology of the Kazakh Institute for Physical Culture /184 (Professor A.D.Bernshteyn, Head), with the object of detecting the local oxygen deficit, while the studies of the GTsOLIFK Biochemical Laboratory (Instructor,

N.I.Volkov) concerned the hypoxia and anaerobic productivity of athletes. We should also mention the studies by the Department of Functional Anatomy, Kiev Institute for Physical Culture (P.V.Gudz' and others) on the morphological alterations in hypoxemia under severe muscular exercise (intramuscular arteriovenous anastomoses, vascular receptors, red blood system, certain hematopoietic organs, myocardium, respiratory muscles).

Considerably less work has been done on the role of hypoxia as a factor encouraging the development of the functional capabilities of the organism. This was the topic used as basis for research, under our supervision, by a group comprising F.A.Iordanskaya, V.A.Matov, O.R.Nemirovich-Danchenko, I.D.Surkina, A.P.Shioshvili, P.M.Babarin and D.A.Chibich'yan, in view of the prime importance of this problem for athletics. With this object, we devised a laboratory model for studying the developmental range of the functional capabilities of the organism; in this device we used a stepwise increase in physical stress under artificially exhausting conditions under inhalation of a low-oxygen mixture, i.e., under the combined action of two factors, namely, motor activity and reduced partial oxygen pressure. We found that the most perfect form of adaptation of the body to muscular activity under hypoxic condition is encountered in highly trained condition of the body, i.e., when the functional capabilities of athletes are improved by systematic training. On the other hand, even a /185
moderate decline in the functional state of the organism, for example, due to excessive fatigue, or inadequate training, produces signs of incoordination of the functions of the somatic and vegetative systems in work under oxygen insufficiency. However, functional incoordination as such is not always due to poor general training; the difference in individual resistance to the hypoxic factor evidently also plays a role. We have advanced the hypothesis that the difference in the tolerance to excessive physical exertion in athletes is largely due to the difference in individual resistance to hypoxia. We noted that the greatest increase in the functional capabilities of the organism is obtained by active adaptation to hypoxic conditions, when muscular effort is combined with an artificial relative oxygen insufficiency (stress hypoxia). Less pronounced shifts are obtained by passive adaptation to hypoxic hypoxia, which in our studies took place in training in the altitude chamber. It has been convincingly shown in special studies that a broadening of the functional capabilities of the body of the medium-distance runner takes place under training conditions with a special regime of respiration (repeated runs, with breath retention). On the whole, muscular work under hypoxic conditions may serve as a satisfactory model for experimental studies on the functional capabilities of the organism. This may be used in medical examinations to determine the individual status of athletic fitness: reactivity, stamina and resistance (toleration) of changes in the /186
internal medium of the organism. These three physiological parameters, determining the physical fitness of human subjects (S.P.Letunov and R.Ye.Motylyanskaya) should be understood as: 1) the capability to intensify the functions in correspondence with the demands made on the organism by a specific motor activity; 2) the ability of the organism to maintain stable homeostasis during more or less prolonged periods of intense muscular work; 3) the tolerance or resistance of the organism to changes in the entire medium under intense muscular activity.

In connection with the impending XIX Olympic Games, the demands for a comprehensive study of the problem of hypoxia and muscular activity are increasing. Investigations should be made not only in model experiments, but also in practi-

cal tests during the usual activities of athletics, especially in mountains of moderate height. Answers are needed to the questions of the training features in various branches of athletics under these conditions and of the dynamics of training stress; another particularly important point is to refine the periods of adaptation and acclimatization in various sports. Special attention must be paid to methods of enhancing the resistance of the organism to hypoxia under conditions of strenuous muscular exertion, using altitude-chamber training together with artificial lowering of the partial oxygen pressure, and determination of the usefulness of certain agents for accelerating the acclimatization. The technique of medical examination for effective control of acclimatization must be refined, and studies on the comparative effectiveness of passive and active adaptation to hypoxia should be continued, including research on the tolerance of hypoxia in certain pathological conditions (tendency to hypertension, certain disorders of neuroregulatory apparatus of the heart, etc.). /187

The solution of these questions demands widespread use of existing research laboratories and the establishment of new ones at training camps in medium-high mountains.

Studies on various questions connected with muscular work under mountain conditions will undoubtedly furnish a valuable contribution to the study of the problem of acclimatization to hypoxia as a whole.

RESPIRATION AND THE OXYGEN REGIME UNDER CONDITIONS OF HYPOXIA

/188

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During adaptation to a reduced partial oxygen pressure, an intensification of the external respiration is of substantial significance. Some authors have stated that an intensification of respiration in hypoxia is only a mechanism of "emergency" adaptation of the organism to the changed gaseous medium, and have even asserted that, on a prolonged stay under reduced atmospheric pressure, the role of this mechanism is gradually lost.

This view does not seem justified, since it has been found that persons permanently living in high mountains at altitudes of 3500 - 4500 m as well as alpinists staying for protracted periods in high mountains under hypoxic conditions, exhibit a marked enhancement in external respiration. Thus, the increase in pulmonary ventilation and the increase in effective alveolar respiration constitute important elements of adaptation to both acute and chronic hypoxia. It is significant that persons adapted to hypoxia (alpinists) have also shown an increase in pulmonary ventilation in the altitude chamber and a greater resistance to high altitudes than the control group.

The considerable individual differences in the degree of hyperventilation under hypoxemic conditions should be given serious attention. This fact is /189 evidently due to the varying sensitivity of the respiratory center to oxygen insufficiency and to carbon dioxide or, more precisely, to their combined action.

To detect individual features of adaptation to hypoxia, we developed a special function test. The test subject was instructed to hyperventilate in the altitude chamber at 5000 m for 10 min, under oxyhemometer control, to maintain the oxygen saturation of the arterial blood at the 90% level. We encountered individual subjects who periodically held their breath and could not adjust to this task. When these subjects inhaled a low-oxygen gas mixture (9 - 10% O_2), the addition of 3% CO_2 to the mixture led to a sharp increase in pulmonary ventilation (considerably greater than in the other subjects) and to a marked improvement of their general condition.

This shows that there exist individuals with a high sensitivity to hypocapnia. Some subjects noted considerable improvement in their condition under hyperventilation, and after such hyperventilation the oxygen saturation of their arterial blood remained at a higher level than before the hyperventilation.

These data, like the observations on subjects during adaptation to reduced barometric pressure in the altitude chamber, permit the conclusion that the increase in pulmonary ventilation is a main factor in the adaptation of the body to oxygen insufficiency. Training, by teaching the subject rational breathing under such conditions, is fully justified since the "training" of the respira-

tory center, i.e., automatic selection of optimum conditions for respiration, takes a long time. /190

During the adaptation of the human organism to reduced atmospheric pressure, there is simultaneous adaptation to hypoxemia and hypocapnia. The individual resistance of various healthy subjects to these two factors is not the same, making it advisable to allow for the individual differences, in working out the conditions of "acclimatization" to high-mountain conditions. Only if this is done can the optimum oxygen regime be established.

DATA ON THE REGULATION OF ZONAL CIRCULATION AND OXYGEN TENSION

/191

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The study of the problem of local (or organ) circulation brings up the question of the blood supply of various regions of the same organ, i.e., of "zonal" circulation and its regulation.

Synchronous registration of the blood supply and oxygen tension in various parts of the myocardium have disclosed zonal variations in these functions, after ligature of a branch of the coronary artery (Sanotskaya).

Our own laboratory studies of the blood supply to the kidneys have shown that, under certain influences, changes occur in different directions in the cortical and medullary layers of the kidney (Lugova).

The brain has proved a good model for studying the regulation of zonal circulation and oxygen tension.

Simultaneous recording of the blood supply and oxygen tension in various parts of the cerebral cortex has shown that adequate stimuli of various distance receptors will selectively cause changes in the blood flow and oxygen tension only in certain regions of the brain. Thus, olfactory stimuli induce corresponding changes in the blood flow and oxygen tension in the olfactory region of the cerebral cortex, while in other zones of the cortex these /192
functions generally do not change. Visual stimuli affect the blood supply and oxygen pressure in the occipital zone (Lugova and Vel'de).

The literature data, together with our own, lead to the conclusion that the observed changes in blood supply and oxygen tension in various zones of the cerebral cortex under adequate stimuli of distance receptors are largely due to a local step-up in metabolism and formation of metabolites (CO_2) which, in a given zone, lower the vascular tonus and increase the zonal circulation and oxygen supply.

SYSTEM OF AUTOMATIC REGULATION OF THE OXYGEN REGIME OF THE ORGANISM

/193

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The oxygen regime is one of the most important factors in maintaining the vital activity of the organs and tissues of the body, and any disturbance in this regime will produce rapid and acute development of functional disorders.

The artificial respiration apparatus, used in clinical practice and experimental work, does not provide for a sufficiently flexible adaptation of the ventilation regime to the needs of the body. Furthermore, the oxygen balance is intimately connected with the activity of a number of other "vital" systems of the organism, including the cardiovascular system which rules the maintenance of optimum conditions for oxygen exchange in the tissues: cardiac output, necessary pressure gradient, etc.

The complexity of the mechanisms for maintaining the oxygen regime of the organism is demonstrated by the following facts:

a) The system of natural regulation in the organism is designed for a wide range of operating conditions of the vital activity of the organism, in connection with complex combinations of environmental conditions.

b) The high requirements as to reliability of maintenance of the constant indices of the internal medium (CIIM) have led to considerable functional reserves.

c) The excessive complexity of a number of mechanisms is an expression of their successive, rather than simultaneous, phylogenetic formation. /194

Accordingly, the practical problem is primarily concerned with the reproduction of the regulatory system for a restricted number of conditions in surgical operations under anesthetic exclusion of most influences and motor reactions.

The present state of the art in cybernetics permits a solution of this problem. The control system for the indices of the internal medium, determining the oxygen regime, on the basis of a feedback complex, permits simulating its natural regulatory mechanisms for practical purposes.

The basic principle of the proposed system for automatic maintenance of the constancy of indices of the internal medium determining the oxygen regime at the assigned level (ASCIIM) makes use of the concept of homeostasis as the basic physiological parameter with respect to which the respiratory, cardiovascular, and other systems of the body play a subordinate, ancillary role. The object

of the system is to maintain the indices of the internal medium (IIM) by compensation or by replacing the organism's own servomechanisms by effector mechanisms, controlled by signals of the state of those parameters of the internal medium that are served by these effectors.

A number of general control principles, characteristic of the organism itself, were used in establishing the ASCIIM. These include:

1. The static principle of the reflex arc, permitting a differentiation, in each of the interrelated control loops, of the receptor, the central portion, and the effector part. /195

2. The principle of joint regulation, expressed by the provision of a single index for the activity of a number of effectors, and by the control of the function of each effector over signals from a number of transmitters, representing the principle of functional linkage of each receptor with each effector.

3. The principle of relative autonomy, of the closed nature of the functional system of control loops entering into the CIIM system.

The ASCIIM in the model of the natural CIIM system performs the role of a functional prothesis, and forms, together with the mechanisms of the CIIM itself, a single mutually complementary functional system of maintaining the physiological parameters (primarily the oxygen regime) at the optimum level. This latter is the object of the duplicate regulation by the natural and artificial CIIM systems. The dynamic variation in the relation between the role of natural and artificial elements in the system is determined by the degree of disturbance of the organism's own regulatory system.

The system uses four types of feedback (FB):

1. The FB of control of the parameters of the internal medium, ensuring a smooth control of the function of the effectors, relative to the assigned level of each parameter.

2. The FB of stepwise switching of the functional regimes, i.e., of the passage of the system to a new function level in connection with the dropout of factors such as the natural rhythm of the heart or the respiratory center, or of the passage of the parameters beyond the limits of permissible values.

3. The FB of control of the assigned level of the parameters of the internal medium, keeping it adequate for the given state of the organism.

4. The compensatory FB (of opposite direction to the ordinary FB), designed to smooth out the reflex oscillations of the function of the effectors and the level of the parameters maintained by them, in connection with the phase shift of the resultant changes of parameters relative to the time of arrival of the corresponding signal from the transmitter. /196

The receptor circuits of the ASCIIM are constructed on the basis of the typical wiring diagram: transmitter - comparator for assigned level of parameter - comparator for critical level of parameter (leading to stepwise switching of the operating regime of the system).

The central unit, i.e., the control system, comprises a unit for switching regimes; several units for evaluating the physiological weight of the connection between each receptor and effector; units for signaling the state of the parameters and the operating regime of the system; and units for adjusting the assigned levels of the parameters and the compensatory feedbacks. If necessary, the control unit may also include programing and electronic computing elements.

The effectors of the system are likewise constructed on the universal wiring diagram: a phase regulator and a compressor providing for smooth automatic regulation of the duration of the phases of forward and backward motion of the gas in this pneumatic control system and of its velocity.

The "executor" devices of the ASCIIM are a diaphragm pump in the effector of the simulated circulation, which meters the introduction of blood preparations and drugs, and the respiratory mask in the effector of artificial respiration. By the aid of these devices, the effectors ensure a smooth regulation /197 of the configuration, volume, duration of expiration (diastole, filling of the metering devices) and inspiration (systole; infusion).

The most important parameters of the internal medium participating in the CIIM system primarily are the following:

1. oxygen tension in the arterial and venous blood and tissues; CO_2 tension in the blood and expired air;
2. volumetric flow of the blood;
3. mean and pulse arterial pressure;
4. body temperature etc.

Depending on the specific objects of the use of the ASCIIM, the circuit of the receptors and effectors can be either contracted or considerably expanded by including receptors of the content of various metabolic ingredients in the liquids and gases of the organism and, as effectors, dosing units of the corresponding preparations, an artificial kidney, etc.

The basic simplicity of the ASCIIM described here is another confirmation of the dialectic concept of the possibility of simplifying a problem as a result of its increasing complexity during detailed study and analysis.

Another trend in the automation of maintenance of the indices of the internal medium, so far only existing on a purely theoretical basis, assumes the automatic production and signaling of symptoms and syndromes requiring medical intervention, automatic evaluation of their significance and selection of the means of intervention, followed by - when this becomes possible - automatic intervention in the state of the internal medium with the object of correcting it.

It should be noted that the effectiveness of such an automated intervention appears extremely doubtful.

In the first place, information on the pathological disorders of the /198
cardiovascular and respiratory systems is not a sound criterion for evaluating and selecting the intervention in basic disturbances of the vital processes, since these systems are servosystems with respect to the constancy of the internal medium and since the task of the physician under critical conditions consists primarily in maintaining this principal parameter, in preventing the development of a vicious circle between ischemia of the CNS and disturbance of the regulation, leading, in the course of a few minutes, to maximum failure of regulation and death. However, disturbances of the vegetative system as a whole reflect not so much the incapacity of the natural effector but rather disturbances in the regulation of its activity; a correction of these disturbances, therefore, is the most effective means of eliminating such acute functional disorders.

In the second place, the tendency - which is essentially of the noncybernetic type - to master (for control purposes) the entire range of pathophysiological patterns in the organism corresponds to the mechanical and materialistic conceptions of Laplacian determinism, reducing the connection between linear causality and interaction to a complete mastery of linear causality. With such an approach, a number of data are required which are not as yet, and will not soon be, available to science; this is mainly because, although objective phenomena can be defined in principle, each of them involves an infinite field of investigation. Accordingly, any attempt to automate the control of a complex group of physiological patterns, on the basis of a method requiring complete mastery of them but without sufficient study of these laws, is doomed to failure, even in principle.

On the contrary, an ASCIIM, consisting of a consecutive cybernetic system whose stability is determined by the interaction of a feedback complex, /199
makes it possible to exclude, from the sphere of automatic analysis, any evaluation of the state of the organs and systems and the methods of their correction, based on relatively simple data relative to the value and direction of the deviation of the vital parameters of the internal medium from a level which, under the given conditions, is optimum. The basic criterion of control is here taken as maintenance of the constant conditions of the internal medium as the principal expression and condition of the vital activity of the organism. Disturbances of secondary significance in the organs and systems, however, which are not corrected by the general normalization of the conditions of the internal medium, will have to be subjected to various additional interventions. The principle of operation of the ASCIIM as a whole corresponds to the idea of cybernetics that it is possible to control the functions of a "black box" without any detailed understanding of its content.

Automatic regulation of functions is supplemented and ensured by the signaling systems and by manual control of the apparatus. The reliability of the ASCIIM is additionally guaranteed by a duplication of its principal units.

PATHWAYS OF OXYGEN SUPPLY TO THE ORGANISM IN ADAPTATION TO CONDITIONS OF THE HIGH TIEN-SHAN

/200

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A stay in high mountains is accompanied by shifts in the physiological functions which, during the initial period, are primarily concerned with maintenance of the initial oxygen regime of the organism (i.e., those existing before stay in the mountains). The character and degree of the shifts depends on the complex influence of mountain conditions. On transfer to a locality not higher than 2.5 - 3.0 km above sea level, the adaptive reactions depend not only on the degree of hypoxia, but also on the temperature conditions, on the intensity of ultraviolet radiation, etc. Therefore, the factor of hypoxia cannot be considered as playing the basic role in the mechanism of the observed shifts of the physiological functions at such altitudes. At still higher altitudes, however, hypoxia does become decisive.

During the initial period of a stay in the mountains, "auxiliary" measures that, to some degree, ensure the "proper" oxygen supply of the organism are mobilized. This is expressed in an increased pulmonary ventilation and in an intensification of the function of the circulatory system which, in turn, leads to an increase in cardiac output, acceleration of the circulation, and decline in venous pressure. The duration and extent of the shifts depend on the features of the geographical region and on the altitude. At altitudes not greater than 2000 m, the shifts are indistinct and persist only for the first few /201 days. At greater altitudes, the changes in the physiological functions are not only more pronounced but also last longer.

In a "proper" oxygen supply of the organism, the increase in the indices of the red blood is of some importance. In the high Tien-Shan, the changes in the quantity of hemoglobin rather than in the number of erythrocytes are of prime significance. The increased filling of the lungs with blood which, according to our data, takes place at altitudes of about 2 km, apparently constitutes an important adaptive shift to high altitudes. The increased permeability of the pulmonary alveolo-capillary membrane is also of substantial importance, as proved by the change in the argyrophilic substance. It is possible that, with a better oxygen supply to the tissues, the increased permeability of the capillaries also has a certain significance (L.A.Preobrazhenskaya).

It seems that neither a study of the partial oxygen pressure in the alveolar air nor a determination of the alveolar ventilation of the lungs, nor a determination of the oxygen content in the arterial and venous blood, nor a study of the function of the circulatory system, etc., can ever solve the problem of the extent to which a reorganization of the physiological functions in high mountains ensures sufficient oxygen supply to the tissues. It is precisely in such re-

organizations of the physical functions of the organism, as they are observed in high mountains, that the oxygen demand of the tissues may also vary. Therefore, it seems important to answer the question as to how far the oxygen demands of the organism, in a given specific situation, are satisfied by the physiological shifts observed at high altitudes. This question may be best answered, as suggested by G.Ye.Derviz, by determining the amount of partial oxidation /202 products accumulated in the organism. It is easy to imagine that, if there is a discrepancy between the oxygen required and that supplied, the partial oxidation products of the metabolism will accumulate in excessive quantities. Our data show that, during the first days of a stay in high mountains, there is a certain shift of partially oxidized metabolites at altitudes of 2000 m and higher.

An increasing number of references has appeared in the literature in favor of the view that the thyroid gland participates in the oxygen supply of the organism. Thus, the observations by Yu.V.Sergeyev and Grandjean on human subjects, and of I.N.Kantorovich on mice, have shown that a stay in high mountains is accompanied by a decrease in the iodine-absorbing function of the thyroid gland. The studies of Stresku et al. have shown that a muscular stress, in the form of swimming, inhibits the output of hormones by the animal thyroid. All these data permit the hypothesis that, under the action of relatively high degrees of hypoxia, the organism apparently mobilizes reactions of a dual nature. Some of these tend to supply the organism with the "proper" amount of oxygen (intensification of the function of the circulatory system, respiration, certain enzymatic systems, increase in the red-blood indices, etc.), while others tend to lower the oxygen demand of the tissues. Reactions of the second kind apparently, at least to a certain extent, measure the most stressed work of the circulatory and respiratory systems, etc. In this connection, the question of the role of reorganization of the endocrine function in the reaction to adaptation to high mountains should be specially investigated.

The above changes in the physiological functions occur during a brief stay in the mountains, when the influence of hypoxia on the organism is dominant. /203

The situation is completely different in the case of a prolonged stay in the mountains (for many years). Here, besides hypoxia, the living conditions, nutrition, geochemical factors, etc., also affect the physiological functions. Nevertheless, the shifts in physiological functions at relatively great altitudes (above 3 - 3.5 km) are primarily determined by the influence of hypoxia. As shown by our studies, the "proper" oxygen supply of aborigines is apparently accomplished by a reorganization of physiological reactions on a different level. In mountain dwellers, no intensification of the function of the circulatory system is noted: the cardiac output remains in the normal range, the blood stream is slowed, and the venous pressure increased. The shifts of the ventilating function are less pronounced. At the same time, the amount of hemoglobin is increased. As shown in observations by L.A.Preobrazhenskaya, mountain dwellers exhibit an increased capillary permeability. Consequently, in permanent mountain residents, a minor rise in the ventilating function of the lungs, an increase in the amount of hemoglobin, and perhaps an increase in the capillary permeability, may be of some significance in the "proper" oxygen supply of the organism.

In permanent residents of high-mountain areas (up to 3.5 km altitude) a

decline in the basal metabolism is noted. Most likely, this is connected with the depressive reorganization of the thyroid function. This apparently decreases the oxygen demand of the tissues, so that the functions of the respiratory and circulatory systems are not so greatly intensified. Perhaps the decrease in the energy consumption is accomplished by a reorganization of the /204 processes of intracellular metabolism, by changes in the rate of enzymatic reactions, and the like. These questions require further study and development.

Thus, the data accumulated up to now provide evidence of the existence, during prolonged acclimatization, of adaptive reorganizations of physiological functions accomplished on the tissue level.

REGIME OF EXTERNAL RESPIRATION IN ATHLETES DURING MUSCULAR ACTIVITY OF CYCLIC TYPE

/205

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The comparative efficiency of various regimes of respiration during muscular exercise of various degrees of intensity was studied in this paper. In particular, we were concerned with the features of respiration through the mouth and through the nose, and of respiration at various ratios of rate and depth.

We found that the maximum pulmonary ventilation (MPV) in breathing through the nose was only one half to one third as great as in breathing through the mounth, while the maximum oxygen consumption (MOC) was 25 - 35% lower. Thus, in intense muscular work breathing through the nose cannot ensure sufficient pulmonary ventilation because of the great resistance of the nasal cavities to the flow of inspired and expired air.

We compared the MPV in respiration at a frequency of 10 - 150/min with the maximum depth for the corresponding rate. The highest values of the MPV were found in the range of 70 to 120 resp/min, and the lowest at 10 - 20 resp/min.

The respiratory rate was visually estimated in 77 runners and on various sections of a cross-country race. A rate of 30 - 40 in 2 min was found in 2.9% of the cases; a rate of 41 - 50 in 5.8% of the cases; of 51 - 60 in 32.5%; /206
of 61 - 70 in 35.3%; of 71 - 80 in 20.6%; and of 81 - 90 in 2.9%. No respiratory rates below 30 or above 90 per min were observed.

During muscular work, at an intensity at which the MOC was reached, the subjects breathed at varying rates and depths of respiration. The highest values of the MOC were reached at a respiratory rate of 50 - 80 per min, somewhat lower at 35 - 45 per min (the difference between these values was statistically unreliable) and still lower at rates of 20 - 30, or else higher than 80 per min. In highly trained skiers, we later repeatedly determined the MOC at natural respiratory rate (using a valve of 36 - 46 per min) and at forced respiration (rate 50 - 80 per min). The MOC obtained in the former case was 66.7 mℓ/kg and in the latter, 67.3 mℓ/kg (difference statistically unreliable).

Thus, the most effective supply of the body with oxygen during intense dynamic work occurs at respiratory rates of 40 - 80 per min and at 50 - 25% of the vital capacity (VC). The individual values fluctuated over a wide range. In one and the same person, the MOC may be relatively equal at a different ratio of rate to depth of respiration (for instance, rate 40 and depth 50% of VC; or rate 80 and depth 25% of VC).

The opinion that deep and slow respiration is preferable is widespread. Our data show that, in the first place, the MOC may fail to vary on extensive fluctuations in the rate and depth of respiration and that, in the second place,

despite the apparent advantage of slow and deep respiration, athletes during /207
intense work mostly breath at a rate of 60 - 80 per min and at a depth of 30 - 40% of VC. The electromyogram (EMG) of certain muscles participating in forced breathing showed that these muscles begin to function at depths of 30 - 40% of VC or higher. Apparently, it is advantageous to the body to establish respiration by the respiratory muscles themselves, releasing the skeletal musculature for specific motor activity. It might well be that this is the reason for the fact that, during muscular work, the respiratory volume, after once reaching 30 - 40% of VC, will no longer vary substantially, whereas the increase or decrease in ventilation - to match the fluctuating power output - take place primarily by varying the respiratory rate. In low-intensity work, this is 25 - 35 per min, while in near-extreme and in extreme work it reaches 60 - 110 per min.

HISTOCHEMICAL STUDY OF BLOOD AND LIVER CELLS AT PHYSICAL STRESS UNDER HYPOXIC CONDITIONS

/208

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The structure as well as the physical and chemical activity of cells are topics that increasingly attract the attention of research workers. Determination of the nucleic acids yields data not only on the nature of the metabolic processes at the cellular level and the state of hemopoiesis but also on the mechanism of immunity. The enzyme content, such as peroxidase, oxidase, etc., permits us to characterize the redox processes in the organism. A histochemical study of intracellular processes offers an approach to an evaluation of the degree and character of the changes and regulation of the processes of recovery, caused by various factors. The object of the present work was a histochemical study of the ribonucleic acid content in the cells of the blood, liver, and heart, and the enzymatic activity in the blood cells. The morphology of the blood and the phagocytic power of its leukocytes were also investigated.

As experimental model, we used the swimming of mice (submerged) from 30 to 90 min at 28 to 30°C. Some of the animals were sacrificed after repeated swims, others were trained for 3 weeks (swimming 3 times per week). In all there /209
were 60 mice, weighing 18 - 20 gm, divided into four groups. In the first, or control group (without swimming), we found that the indices of hemopoiesis, phagocytic and enzymatic activity of the blood were close to normal. In the liver cells, the RNA was for the most part localized along the periphery; the heart muscles stained uniformly but contained no RNA. It is known from the literature that RNA is found only in the heart muscle of rats (F.V.Shtraub).

The mice of the second group, after submerged swimming for 30 min, showed an activation of the hematopneic, phagocytic, and catalase indices. Thus, the activity of the phagocytes increased from 3.22 ± 0.29 (at rest) to 5.61 ± 1.60, while the intensity rose from 0.67 ± 0.007 to 1.60 ± 0.07. The histochemical index of peroxidase activity increased from 1.53 ± 0.07 to 1.71 ± 0.001. At this load, occasional blood cells saturated with RNA were encountered, and the RNA level of the liver cells started to vary: All liver cells were filled quite uniformly with RNA in the form of reddish small and large granular blocks. In the heart muscle, RNA appeared in the form of a roseate powdery dust (in individual myofibrils).

After extensive stress (third group), we noted a decline in the indices of hemopoiesis and leucopoiesis and considerable changes in blood morphology. We also noted depression of the phagocytic and enzymatic activity of the cells. Thus, the activity of phagocytosis declined to 2.30 ± 0.16, and the intensity to 0.38 ± 0.02, while the histochemical index declined from 1.53 ± 0.09 to 0.67 ± 0.05. Juvenile cells appeared, some of them saturated with RNA, but many

others containing none. There was considerably less RNA in the liver cells than after a 30-min swim, but more than in the controls. No RNA was found in the /210 cardiac myofibrils.

In the trained mice (fourth group), the changes in blood morphology were close to those in Group 3. However, the protective and enzymatic activity of the blood cells was higher than in the untrained mice. RNA was found in the protoplasm of many leukocytes. The trained mice had more RNA in the liver cells than the untrained animals. There was likewise no RNA in the heart muscle.

Thus, the histochemical study of the cells yields information on the degree of strain in the various systems. Higher stresses, under conditions of relative hypoxia, induced changes greater than those of the physiological zones: depression of the functions of hemopoiesis, phagocytic, and enzymatic activity of the blood cells. In addition, the absence of migration of RNA into the protoplasm of some cells of the blood and liver, at this stress, proved the decline in the intracellular metabolic processes, i.e., a disturbance of the rate of protein synthesis.

Small stresses in trained mice activated defensive-adaptive reactions. An increase in the RNA content was noted in the blood cells and liver cells of mice, with concomitant cell renewal. These immunological and histochemical changes of a proliferative and metabolic character can be regarded as the morphological substrate of the adaptive reactions of the organism. It is well known that morphological changes precede the appearance of antibodies, as an important factor of immunity.

THERAPEUTIC EFFECT OF ARTIFICIAL CIRCULATION IN HYPOXIA OF THE MYOCARDIUM AND BRAIN

/211

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Hypoxia of the myocardium and brain is a fundamental symptom of advanced acute cardiopulmonary insufficiency, which we induced experimentally by two methods. In the first series of experiments, acute cardiopulmonary insufficiency was induced by application of tourniquets to the pulmonary roots, except at the lower part of the left lung whose respiration was artificially continued during the entire experiment.

From the time the tourniquets were tightened to manifestation of extreme symptoms of hypoxia of the myocardium and brain, an average of 26 min elapsed (this time varied from 9 to 70 min). During this period, judging from the ECG, generally arrhythmia, ventricular extrasystoles, and paroxysmal tachycardia occurred first, followed by increasing symptoms of acute coronary insufficiency, in some experiments going as far as atrioventricular fibrillation, sharp slowing of the rate, ventricular fibrillation, and cardiac arrest.

The EEG simultaneously showed a decline in bioelectric activity of the brain, the appearance of slow rhythms and, at the peak of cardiac insufficiency, arrest of brain activity.

Against the background of this severe hypoxia of the myocardium and brain, we tested the therapeutic effect of derivative circulation, by means of "heart-lung" machines of the "Rygg-Kywsgaard-3", "ISL-2", and "ISKhF-1" types. /212

Artificial circulation was maintained by the following arrangement: The venous blood was drained into the oxygenator by catheters introduced through the jugular and femoral veins to the level of the mouths of the venae cava; the arterialized blood was collected by a pump and forced into the femoral artery. During the derivative circulation the tourniquets were left on the pulmonary roots. However, despite operation of this pathogenetic mechanism for periods of 5 to 116 min (with an average of 36 min), this shunt circulation did eliminate hypoxia of the heart and brain and normalize their functional indices.

In the second series of experiments, acute cardiopulmonary insufficiency was induced, without thoracotomy, by active pulmonary hyperventilation, using air containing a small amount of ether.

In this series, hypocapnic hypoxia of the brain and myocardium took from 12 to 42 min to develop (on the average, hypoxia reached its maximum within 24 min). The hypoxia of the brain was not as severe as in the preceding series,

although there were always manifestations of coronary insufficiency and decreased cerebral activity.

The therapeutic effect of artificial circulation, using the above method or the method of arteriovenous perfusion without blood oxygenation, was manifested in 3 to 60 min (on the average, in 40 min).

In conclusion, we should mention that, as soon as possible after the therapeutic effect of artificial circulation has been established and the activity of both heart and brain has been normalized, the perfusion should be stopped /213 in view of the fact that, on further prolongation, all symptoms of circulatory-respiratory disorders and hypoxia will reappear; these would constitute a pathological reaction of the organism to the artificial circulation itself.

OXYGENATION OF THE BLOOD AND TISSUES OF THE BRAIN DURING RESPIRATION AT EXCESS PRESSURE IN A RAREFIED ATMOSPHERE

/214

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We studied the oxygen supply of the organism of animals (dogs) during respiration under positive pressure, using systems of compensation of varying effectiveness under sea-level and altitude conditions. The pO_2 was determined polarographically in the blood (in mm Hg) and in the brain tissues (in relative units, in percent of the initial value). In some of the experiments, we investigated the course of the pCO_2 of the blood. As a control of the general state of the animal, we took a pneumogram, an EMG of the muscles, and an ECG.

We found that the oxygen tension in the blood and tissues of the brain depends on the alveolar pO_2, on the level of positive pressure in the lungs, and on the effectiveness of the compensating systems at sea level and at high altitudes.

In respiration of oxygen under normal pressure at "ground level", the pO_2 in the lungs rose to 670 mm Hg (by a factor of 6) and in the arterial blood to 465 mm Hg (by a factor of 5); the oxygen tension in the tissues of the brain increased only 1.5 - 2 times. Thus, there was a marked discrepancy between the alveolar pO_2 and the blood pO_2, and, particularly, in the brain tissues.

Inhalation of oxygen under excess pressures up to 30 mm Hg without external counterpressure induces a subsequent increase in arterial pO_2 (to 491 mm Hg) with a simultaneous decline in venous pO_2 to 39.5 mm Hg, against an initial /215 level of 55 mm Hg. There is an accumulation of CO_2 in the venous blood, accompanied by marked changes in hemodynamics and respiration, indicating a restricted inflow of blood to the right heart and complication of exhalation. The O_2 pressure in the brain tissue doubles.

An excess pressure of more than 30 mm Hg usually causes a decline of pO_2 in the brain tissues to below the initial values, indicating a stoppage of the compensatory reactions of hemodynamics and respiration. The spread of the excess pressure, or the application of an effective external counterpressure, will have a leveling effect (but often also leads to a brief sharp "jump" of the lowered pO_2 in the brain tissues) and will smoothen the changes in the cardiovascular and respiratory systems.

A further increase of the intrapulmonary pressure to 200 mm Hg, in combination with an equal external counterpressure, led in most experiments to a greater increase of the pO_2 in the brain tissues than that produced by the inhalation of oxygen under normal pressure. Even in this case, however, the increase of pO_2 in the brain tissues lags behind the increase of pO_2 in the lungs.

Under altitude conditions, no pronounced lag of the pO_2 in the blood and brain tissues behind the alveolar pO_2 is noted. At altitudes above 12,000 m,

at an absolute pressure of 150 mm Hg in the lungs and with effective compensation by external counterpressure, these values correspond to the pO_2 level noted at 4000 m altitude during inhalation of regular air or at 12,000 m during inhalation of oxygen under the pressure of the ambient atmosphere. During inhalation under excess pressure, at 200 mm Hg and altitudes over 10,000 m, the /216 pO_2 in the blood and brain tissues approaches its initial values.

At altitudes of 20,000 - 30,000 m, during respiration under excess pressure, the blood pCO_2 was found to depend on the level of intrapulmonary oxygen pressure. At 150 mm Hg pressure in the lungs, hypocapnia was observed but disappeared when the intrapulmonary pressure was increased to 200 mm Hg.

Hypocapnia during respiration under positive pressure at great altitudes is a consequence of hypoxia rather than of the decreased barometric pressure or the increased intrapulmonary pressure.

CONTRIBUTION TO THE QUESTION OF THE REGULATION OF OXYGEN EXCHANGE UNDER CONDITIONS OF ARTIFICIAL CIRCULATION

/217

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The CO_2 of the blood plays a major role in the regulation of oxygen exchange. This has been proved in investigations of the effect of CO_2 on the rate of oxyhemoglobin dissociation, in studies on the role of CO_2 in the regulation of the respiratory center and cardiovascular system activity, and by experimental results as to the effect of CO_2 on the oxidative processes.

Under conditions of natural respiration and circulation, the activity of the respiratory center, varying under the influence of the gas composition of the blood, may exert a noticeable influence on the level of O_2 and CO_2 in the organism. However, under the conditions of artificial respiration, and also under conditions of extracorporeal blood circulation, this mechanism is cut out. The conditions under which the CO_2 content of the blood decreases are of particular interest here. In this connection, we studied the oxygen exchange during prolonged artificial pulmonary hyperventilation (extending over one hour) and also during artificial blood circulation, in conjunction with hypothermia, under various gas regimes of perfusion.

The experiments were performed on dogs, 12 to 23 kg in weight. The studies on the oxygen exchange during prolonged hyperventilation were made on 17 dogs. The experiments with artificial circulation, in conjunction with moderate hyperventilation, were performed on 19 dogs. In later experiments, we used an alternating gas regime: At 10 - 20 min intervals, the operation with oxygen was replaced by operation with oxygen and carbon dioxide, which in turn was replaced again by operation with oxygen. During the oxygen regime, only oxygen was /218 fed to the oxygenator, while during the oxygen-CO_2 regime, 3.4% of CO_2 was added to the oxygen feed. We measured the oxygen saturation of the arterial and venous blood, the pCO_2, the volume rate of flow of blood through the brain, the brain oxygen consumption, the acid-base equilibrium, the arterial pressure, the ECG, and the EEG.

The results of our studies on the effect of hyperventilation on the animal organism, included the following:

After transition from natural respiration to hyperventilation, we noted in most of our experiments an increase in oxygen saturation of the blood, and a simultaneous decline in pCO_2. This decline, already manifested at the beginning of hyperventilation, amounted in 15 min to 29%, and in 60 min to 50%.

In most of our experiments, this was accompanied by a decline in the blood flow through the brain, an increase in the arteriovenous oxygen difference, and a gradual increase in metabolic acidosis; we observed an increase or decrease in oxygen consumption of the brain in the same number of cases. We also noted a

drop in arterial blood pressure to 40 mm Hg and less, concomitant with changes in the ECG and EEG indicating development of hypoxia in both heart and brain.

Of the 17 dogs on which experiments with hyperventilation were made, eight died. Three of these died because the apnea continued after hyperventilation had been stopped, so that the activity of the respiratory center was not restored; in the other five, independent respiration had been restored after the end of hyperventilation, but they all died during the first days after the /219
experiment.

Our studies in this series of experiments are of interest in the following directions:

1. They showed that, as a result of hyperventilational hypocapnia, the oxygen consumption of the brain increased in half of our experiments. The literature contains statements that hypocapnia will lead to an increase in the general level of oxidative processes. Our data show that, under the influence of hypocapnia, the oxygen consumption of the brain increases. That this was observed in only 50% of the cases was apparently due to the degree of hypoxia involved as well as to the depth of narcosis, both of which varied during the course of the experiment.

2. Prolonged hyperventilation induces cardiovascular and respiratory insufficiency, which may lead to death immediately after the hyperventilation is stopped or at various periods thereafter, ranging from several minutes to several hours.

3. Our data permit us to regard the complex of changes (which set in as a result of hyperventilational hypocapnia) as a model of cardiovascular and respiratory insufficiency, which may serve as basis for devising measures for prophylaxis and elimination of hypoxia.

In the experiments with artificial circulation, in conjunction with hypothermia (30 - 22° C in the esophagus), changes in the gas composition of perfusion also induced corresponding fluctuations of the pCO_2 in the arterial blood. In the oxygen regime of perfusion, the pCO_2 of the arterial blood fluctuated from 32 to 35.6 mm Hg, and in the oxygen-CO_2 regime from 42.8 to 49 mm Hg.

In most of our experiments, on transition from operation with oxygen /220
to operation with oxygen and carbon dioxide in the perfusion, the blood flow through the brain increased as did also the oxygen consumption of the brain whereas, on transition from the oxygen-CO_2 regime to the oxygen regime, the volume rate of blood flow through the brain and the oxygen consumption of the brain both decreased. Our data seem to indicate that an addition of CO_2 to the oxygen, in experiments with artificial circulation and hypothermia, facilitates the oxygen uptake of the brain which had undergone oxygen starvation under the conditions of oxygen perfusion. This agrees with the ideas of the role played by CO_2 in the dissociation of oxyhemoglobin, especially under conditions of hypothermia.

These studies have shown that regulation of the gas content may be one means of controlling perfusion so as to ensure adequate artificial circulation.

DYNAMICS OF CHANGES IN THE OXYGEN TENSION UNDER VARIOUS GAS CONTENTS OF THE ARTIFICIAL CIRCULATION EQUIPMENT

/221

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The variations in oxygen tension in the tissues of the brain, heart, and muscles of the extremities were studied by the polarographic method. The experiments were performed on dogs 14 to 30 kg in weight, under conditions of artificial circulation. In all, 74 experiments were performed.

The object was to investigate the variations in oxygen tension in various organs, in its dependence on the gas content in perfusion during a prolonged artificial blood circulation (1 - 2 hrs). The experiments were run at normal temperature and under hypothermia. In all, three series of experiments were performed.

The studies showed that the oxygen tension in the tissues of the brain, heart, and muscles of the extremities depends on the gas composition of the perfusion.

In the oxygen regime, both at normal body temperature and in hypothermia, there was a constant drop in oxygen tension in the tissues below the initial level, throughout an experiment extending over 1 - 2 hrs.

At normal body temperature, the oxygen tension had declined, on the average, by the end of the experiment:

a) by 12% in the brain, 20% in the myocardium, and 29% in the skeletal muscles;
b) at hypothermia, the oxygen tension dropped by 8% in the brain, 12% in the myocardium, and 20% in the skeletal muscles.

/222

Under continuous prolonged operation at oxygen plus carbon dioxide, the oxygen tension, throughout the experiment with normal body temperature, increased by 12% in the brain and by 22% in the myocardium; with hypothermia, it increased by 15% in the brain and by 30% in the myocardium, while a decline of 25% was noted in the muscles of the extremities.

In the third series of experiments using alternating gas regimes, on transition from operation with oxygen to oxygen plus carbon dioxide, we noted a certain increase in the pO_2 of the brain and heart tissues; on transition from oxygen plus carbon dioxide to oxygen operation, there was a drop in oxygen tension.

On transition from pure oxygen to oxygen plus CO_2, at normal body temperature, the oxygen tension in the brain tissues increased by 8% and in the myocardium by 15%, while no reliable increase in pO_2 was noted in the skeletal muscles.

In hypothermia, under the above conditions, the oxygen tension in the brain increased by 22% and in the myocardium by 30%, while the pO_2 dropped by 32% in the skeletal muscles.

On transition from the oxygen plus CO_2 to pure oxygen at normal body temperature, the oxygen tension in the brain tissues remained within the original range or dropped by 8% in some of the experiments; in the myocardium it declined by 19%, while the drop in pO_2 was pronounced in the skeletal muscles, namely, 40%.

In hypothermia, the oxygen tension in the brain tissue dropped by 19%, in the myocardium,by 13%, while the pO_2 dropped by 30% in the skeletal muscles. /223

The changes in pO_2 as a function of the gas conditions of the perfusion were accompanied by regular variations in the blood flow of the brain and of the vascular tonus in the rear extremities.

On transition from oxygen to oxygen plus CO_2, we noted an increase in blood flow through the brain and an increase in vascular tonus of the extremities. On transition from oxygen plus CO_2 to oxygen, the blood flow through the brain decreased and the vascular tonus of the extremities became weaker (V.S.Rayevskiy, G.A.Myamlina, L.A.Sumbatov, Ye.N.Ashcheulova, L.Ye.Kramarenko, O.P.Shalybkova, and Ye.R.Soboleva).

The variations in oxygen tension in the tissues with the gas composition of the perfusion, noted by us, obviously are due to reactions of the vascular system in connection with the redistribution of blood mainly concerned with supplying blood first to the vital organs; they are also due to the effect of CO_2 on the oxyhemoglobin dissociation rate.

ON THE MECHANISM OF DISTURBANCE OF THE OXYGEN REGIME OF THE HEART IN CORONARY OCCLUSION

/224

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A result of acute coronary occlusion is the interruption of oxygen supply and of readily utilized oxidation substrates in a circumscribed area of the heart.

The restriction of the influx of substrates is compensated by the utilization of the reserve source of energy in the heart, glycogen, and therefore that phase of metabolism that concludes with the formation of reduced diphosphopyridine nucleotide (DPPN) is not substantially impaired. The oxygen insufficiency leads to more severe changes, since the heart oxygen reserves are very limited and are sufficient only for 5 - 6 cardiac cycles. In this connection, the phase of metabolism concerned with transfer of hydrogen from the DPPN to the molecular oxygen is depressed.

Owing to inadequate disturbances of these two metabolic phases, the ratio of the oxidized to the reduced form in the myocardium varies. It is well known that this ratio is characterized by the value of the redox potential (ROP) whose fluctuations constitute an important index characterizing the state of the redox processes in the heart during myocardial infarct.

Reflecting the intensity of the redox processes, the ROP will permit only an indirect judgment as to the oxygen tension in the myocardium; therefore, /225 for a more complete characterization of the state of oxygen conditions in the heart in myocardial infarct, the oxygen pressure (pO_2) must be simultaneously determined.

In the case of changes in the ROP of the myocardium in coronary occlusion, only the determination of redox systems, such as $\frac{\text{lactic acid}}{\text{pyruvic acid}}$, etc., is of selective importance.

The object of the present work was to observe the variations in pO_2 and ROP during the acute stage of myocardial infarct and to establish the value of the redox system $\frac{\text{lactic acid}}{\text{pyruvic acid}}$ (L/p) in the total ROP of the myocardium.

To accomplish this, we developed - in collaboration with B.P.Rastorguyev - a technique of potentiometric measurement and recording of the myocardial ROP in vivo. The pO_2 of the myocardium was synchronously measured and recorded by the polarographic method. To study the mechanism of variation of the myocardial ROP in synchronism with its recording, we investigated the ROP of the L/p system and the activity of the cytochrome system of the mitochondria at an ischemic

focus.

The oxygen tension and the ROP were studied after ligature of the coronary artery, at the focus of the ischemia and in the intact zone, on 34 dogs. The animals were narcotized with a mixture of urethane and chloralose; the thorax was opened on the median line, and the animals were put on artificial respiration of atmospheric air. After opening the pericardium, electrodes were inserted at the future focus of ischemia and at the intact zone of the heart, /226 to record the local variations in oxygen tension, the ROP, and the electrogram (EG) after ligature of the anterior descending artery.

Our study showed that no substantial changes had occurred in the pO_2, ROP, and EG in the intact departments of the heart, while in the zone of ischemia there was a steady drop in pO_2 and in the ROP, at increasing monophasicity of the EG. The decrease in pO_2, observed at the ischemic focus, was in agreement with the literature data (Rayskina et al., 1963; Marshak, 1963; Sanotskaya, 1963; Sayen and others, 1954, 1958; Miyashita, 1962) and was a consequence of the interruption of oxygen supply from the blood.

The drop in the total ROP is apparently due to two causes: depression of the oxidation rate in the mitochondria which should result in a decrease in concentration of the oxidized forms, and activation of glycolysis in the cytoplasm which leads to an increase in concentration of the reduced forms.

To define the role played by the L/p redox system in the decrease of the total ROP of the heart, the lactic and pyruvic acid levels were studied in 21 cat experiments, and the redox potential of the L/p system was calculated. Gudbjornsson and Bing (1962) as well as Nägle, Hockerst, and Bögelmann (1963) studied the ROP of the L/p system in the coronary arterial and venous blood. On ligation of the coronary artery and after inducing hypoxia in dogs, these authors found a decrease in the ROP of this system, in the blood of the coronary sinus. In our own experiments, the ROP of the L/p system was studied in the tissues of the ischemic and non-ischemic zones of the myocardium, a total of 5 and 30 min after ligature of the coronary artery, with simultaneous recording of the total ROP. No substantial variations in the total ROP and the ROP calcu- /227 lated for the L/p system could be detected in the intact zone of the heart. At the ischemic focus, 5 min after ligature, the ROP of the L/p system declined sharply but rose again after 30 min (without, however, reaching the original level), while the total ROP declined steadily.

These data permit the hypothesis that the decline in total ROP immediately after ligature is due primarily to an activation of glycolysis in the cytoplasm. After 30 min, when the glycogen reserves in the myocardium have been largely exhausted, the glycolysis slows down; the decline in the total ROP in this phase evidently is a result of the depression of redox processes in the mitochondria. To define this situation, we collaborated with V.G.Leonova, a staff member of the Institute of Radiation Biology - using differential spectrophotography - in studies on the redox capacity of the cytochromes isolated from the intact and ischemic departments of the cat heart, 20 min after ligature of the coronary artery, and delivered under optimum conditions. No differences were observed between the redox power of the enzymes isolated from the ischemic and non-ischemic zones. At the early stages of ischemia, evidently, the depression of

the redox processes in the mitochondria is not connected with structural changes in the enzymes of the cytochrome chain and is due only to oxygen insufficiency.

These data reveal two features in the mechanism of disturbance of the oxygen regime of the heart in the earlier stages, following ligature of the coronary artery. The first is a difference in mechanism of decrease of the ROP at /228 different intervals after the appearance of ischemia. Immediately after ligature of the coronary artery, the decline in ROP is apparently due to an activation of glycolysis, while in later periods it is caused by the inhibition of oxidation in the mitochondria. The second feature is that the disturbance of the redox processes in the mitochondria probably is not connected with structural changes of the enzymes of the cytochrome system but rather is due to conditions that prevent a manifestation of their catalytic properties.

The results point toward the effectiveness of therapeutic measures for normalizing the redox processes in the acute stage of myocardial infarct.

CONTRIBUTION TO THE ANALYSIS OF THE MECHANISM OF THE ACTION OF HYPOXIA AND HYPERCAPNIA ON THE CENTRAL NERVOUS SYSTEM

/229

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The finding of a series of similar functional shifts in oxygen starvation of the organism and in hypercapnia has convinced many authors that these two pathological states are synonymous and that hypercapnia represents merely a special case of oxygen starvation (P.M.Al'bitskiy et al.).

In this paper an attempt is made to analyze, under comparable conditions, the effects of various degrees of hypoxia (1 - 16% O_2 in the inspired air) and hypercapnia (5 - 30% CO_2) on the functional state of the central nervous system of rabbits, white rats, and white mice.

The experiments showed that, even on inhalation of subnarcotic concentrations of CO_2 (10 - 20%) compatible with prolonged maintenance of vital functions, in the absence of any substantial functional disorders and at normal oxyhemoglobin levels of the blood, the animals showed a marked weakening and practically complete disappearance of the electric activity of the brain.

This effect extended not only to the spontaneous activity of various regions of the brain but also to the "induced" potentials (local convulsive discharges, thalamocortical "involvement rhythm") as well as to the spontaneous and electroconvulsive discharges in a region of the cortex completely isolated from all nervous connections.

In contrast, a decrease in the oxygen content of the air to 10% caused /230
no major changes in the EEG; however, when this dropped to 5 - 7%, the high-amplitude slow waves began to dominate. Only in extreme hypoxia (4 - 5% O_2), causing a decrease in blood Hb by 50% and more and accompanied by severe disturbance of hemodynamics, disorders in respiration, and rapid death, did a depression and fading of the EEG occur. Judging from the EEG data, the sensitivity of the central nervous system to threshold variations in the CO_2 tension is considerably higher than its sensitivity to hypoxia. At the same time, the resistance of the CNS to the detrimental effect of extreme hypoxia is very much lower than that to hypercapnia.

A considerable difference in the action of these two pathogenic factors was also observed with respect to the energy indices of the brain tissue. While inhalation of 5 and 7% O_2 caused a considerable decline in the macroergic phosphate (ATP and CP) in the rat brain, and a sharp rise in lactic acid and inorganic phosphorus, the inhalation of 20 and 30% CO_2 caused no change in ATP, CP or NP, while the lactic acid level declined considerably. An addition of 5% CO_2 to hypoxic mixtures normalized the shifts of the organophosphorus meta-

bolism.

These data indicate a fundamental difference between the mechanisms of the depression of the central nervous system in hypoxia and hypercapnia.

Several possible mechanisms of these changes are discussed in the paper.

THE EFFECT OF PRELIMINARY ATHLETIC TRAINING ON ACCLIMATIZATION IN MOUNTAINS

/231

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According to the doctrine of I.M.Sechenov and I.P.Pavlov, the study of the intact organism should be performed in inseparable connection with the environment. Consequently, studies on alpinism are best performed directly in the mountains, in alpine huts, on climbs, and in expeditions.

The basic factor, of continuous action under these conditions, is the decreased partial oxygen pressure which affects a number of physiological processes and may lead to disorders. Athletic training and adaptation to high-mountain climate is of great importance in developing resistance to oxygen want. Until now, no extensive studies have been made on alpinists, comparable to those made on athletes of various backgrounds and qualification during training and competitions.

On this basis, we posed the problem of attempting - by studying the principal physiological indices and the application of certain tests - to verify the effect of preliminary physical training on the acclimatization during high-mountain climbs.

Our experimental material covers 1032 tests on 174 subjects, conducted in the summer at the "Talgar" mountaineering camp in the Tien-Shan mountains at elevations of 2650 m above sea level and in the "Donbay" hut in the Caucasus /232 mountains at an elevation of 1650 m. Most of the alpinists stayed in the camp for 20 days, making periodic climbs to altitudes of 4000 - 5000 m above sea level which corresponded to active acclimatization.

The following methods were used: In one series, we studied the degree of oxygen saturation of the blood on the oxyhemometer at maximum breath retention (at normal inspiration) to standard load, during the retention and after its completion. At the end of the breath-holding period, cyanosis of the mucous membranes and epidermis usually occurred, occasionally accompanied by tremor. These studies were made on two groups of subjects: 50 trained subjects and 26 subjects untrained to physical stress. In some of these subjects, the hemoglobin level of the blood was also measured by the Sala method at the beginning and end of the stay at the camp.

In another series, we determined the resistance to hypoxia, when breathing into a Krog respirator, filled with air. The degree of resistance was defined as the maximum period of breathing into this device before signs of oxygen want set in: cyanosis or tremor, change in handwriting. During the hypoxic test, both frequency and amplitude of respiration were recorded, the pulse was taken every minute, and the handwriting was checked. In all, 60 subjects were studied by this method, 43 trained subjects and 17 untrained subjects (control group).

In a third series, we determined the resistance to hypoxia by the same method, with simultaneous oxyhemography. We also measured the blood hemoglobin level in these subjects. The studies were performed at the beginning of the stay at the camp, before an ascent, after it, and at the end of the stay at the camp. The group comprised 38 subjects with previous athletic training, of /233 whom 21 were adapted to the high-mountain climate, while the others were not. All data of the studies were worked up statistically by the Wilkinson and Stuart-Fisher methods.

As a result of our investigations based on the above methods, we drew the following conclusions:

1. The compensatory reactions of the organism developed during physical training resemble, in their nature, the adaptive reorganization under the effect of hypoxia. They also constitute the basis of the more rapid process of adaptation to altitude in persons with athletic training.

2. Athletic training in the lowland, in addition to other physical qualities, developed greater endurance permitting more ready adaptation to hypoxic conditions and more rapid acclimatization to high mountains.

3. Trained athletes (various types of athletics) are more capable to withstand the physical exertion involved in mountain climbing.

4. Untrained subjects, without previous physical preparation, are subject to excessive stresses when staying in high-mountain regions.

5. In untrained subjects, who do not practice sports and have no physical preparation before entering the mountains, the greater physical stress produced by alpinism (even in the case of active acclimatization) leads to impairment of the physiological functions.

6. Fatigue due to physical stress during approach and ascent decreases the resistance of the organism to hypoxic effects; this must be taken into account in planning the time schedule of ascents and other types of muscular activity /234 in high-mountain areas.

7. Subjects without adequate physical preparation should not be allowed to participate in alpinism or other forms of physical exertion under high-mountain conditions (geologists, geographers, topographers, geodesists, speleologists, border guards, and the like).

8. Alpinists, during the preparatory period of training, must practice forms of athletics involving prolonged exercise of moderate or high intensity. Skiing in winter and cross-country runs in spring are the best examples of such forms.

9. Good physical training, with simultaneous acclimatization to high mountains, leads to maximum physical and hypoxic endurance, which may be useful for more effective training of top-notch athletes.

DYNAMICS OF ZONAL VARIATION OF OXYGEN TENSION IN THE MYOCARDIUM IN LOCAL ISCHEMIA

/235

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In acute and chronic dog experiments, the variations in oxygen tension in the myocardial tissue, with ligature of the coronary artery, were studied polarographically. The oxygen tension was synchronously investigated in three zones of the myocardium, the ischemic zone, the directly adjoining zone, and a zone distal from the ischemic focus.

After ligature of the coronary artery, there was a sharp drop in oxygen tension, not only in the zone supplied by the ligated artery but also in the adjacent regions of the myocardium. In the acute experiments, during the next 2 - 4 hrs after ligature, the oxygen tension did not recover in these zones. In some of the dogs studied without narcosis, the oxygen tension in the boundary zone was completely or partially restored during the first hour after ligature.

The reaction in a region of the myocardium distal from the ischemic focus, directly after ligature, was less uniform in the acute experiments: In some of the experiments, the oxygen tension in the myocardial tissues remained unchanged, in others it increased somewhat, and in still others it decreased somewhat. /236 The unanesthetized dogs showed an increase in oxygen tension in the myocardial zone distal from the ischemic focus after ligature, in more than half of the experiments.

Before ligature, the inhalation of oxygen always increased the oxygen tension in the myocardium. After ligature, the reaction to oxygen inhalation varied in the zones of the myocardium: In the ischemic region, there was no reaction in most cases for several hours after ligature, indicating complete disconnection of the blood supply to this region. In the region of the myocardium adjoining the ischemic focus, oxygen inhalation always induced a certain increase in oxygen tension, but this reaction was considerably less pronounced than that before ligature.

The justification of using the degree of change in oxygen tension on oxygen inhalation ("oxygen test") for an indirect estimate as to the presence or absence of blood supply to the tissues was confirmed by special experiments in which the blood supply to the tissue was varied at will by the experimenter, by the aid of a perfusion pump, keeping it constant over a predetermined period. The increase in oxygen tension in the tissues after oxygen breathing, in these experiments, was parallel to the variation in blood flow: It increased with increasing delivery of the pump and decreased with decreasing delivery; the reaction to oxygen inhalation disappeared completely when the pump was shut off, proving complete interruption of the blood flow. /237

To clarify the question of restoration of circulation in the ischemic area

of the myocardium, chronic experiments were performed on dogs, with platinum electrodes inserted in the myocardium.

As under the conditions of the acute experiment, for the first 5 - 6 hrs after the ligature of even a small branch of the coronary artery, there were no reactions at all to oxygen inhalation in the ischemic zone; the reaction in the adjacent zone was considerably lower than its original level. This indicates complete stoppage of the blood supply to the ischemic zone and restricted blood supply to the adjacent zone. However, already on the day after ligature of a branch of the coronary artery, a slight increase in oxygen tension after oxygen inhalation appeared in the ischemic zone. With increasing time after ligature of a branch of the coronary artery, the reaction to oxygen inhalation increased in both the ischemic and adjacent zones and exceeded the initial reaction 5 - 6 days after the ligature. This indicates a gradual restoration of the blood supply to these zones.

The investigations yield data on the recovery time for blood supply to the ischemic and adjacent regions of the myocardium. It is shown that, during the first few days after the appearance of an ischemic focus in the myocardium, the ischemic and adjacent zones of the myocardium are again supplied with oxygen. This may be considered the result of a gradual increase in the retrograde blood flow, owing to the opening of previously non-functioning collateral channels.

CONTRIBUTION TO AN ANALYSIS OF THE ROLE OF THE ERYTHRON IN THE REGULATION OF THE OXYGEN REGIME OF THE ORGANISM /238

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The oxygen regime of the organism is expressed by a series of interrelated parameters of the partial pressure and amount of oxygen, measured over its transport path from the lungs to the tissues (N.V.Lauer, A.Z.Kolchinskaya). These parameters permit an evaluation of the general conditions for the progress of the oxygen exchange in the organism. To a certain extent they also give an idea on the functional interrelation of the oxygen transport systems, which include external respiration, the erythron, and blood circulation. These systems regulate the oxygen regime in accordance with the demand of the tissues and the supply of oxygen to the tissues.

We used the term "erythron" as a synonym of the concept "erythrocytic system" in the functional sense assigned to it by G.F.Lang (1939), D.N.Yanovskiy (1957), A.I.Vorob'yev, and I.I.Gitel'zon (1959). The primary role of the erythrocytic mass of the blood is to transport oxygen from the lungs to the tissues. The erythron may affect this process by regulating the oxygen-binding function of the blood. This function is determined by the oxygen-binding activity of the erythrocytes and by their absolute number in the blood stream. The absolute oxygen capacity is the overall index of the state of the oxygen-binding function of the blood. It is defined as the maximum amount of oxygen that can be contained in the entire volume of circulating blood at 100% oxygen saturation.

The relative oxygen capacity, expressed in vol.%, is a less accurate /239 index of this function, due to the fact that this relative oxygen capacity is an index of the oxygen concentration in the blood (at 100% saturation). Therefore this index depends not only on the true variation of the erythrocyte count but also on the relative erythrocytosis associated with thickening of the blood (hemoconcentration). However, the intensity of the oxygen-binding function of the blood varies only with the true shift in the number of erythrocytes. Naturally, one must also take account of their qualitative composition in this respect.

Under the conditions of normal life, the absolute oxygen capacity of the blood is relatively constant. This is ensured mainly by regulation of the erythrocyte balance. On disturbance of the conditions of gas exchange, the erythrocyte level of the blood may vary. When this occurs, erythrocytosis may rapidly develop, due to the reflex redistributive reactions of the deposit-flow type. The slow and gradual variation of the number of erythrocytes in the blood is produced by a highly complex neurohumoral control of the activity of erythropoiesis and erythrolysis.

The adaptive changes in the respiratory surface of the blood belong to the

systemic regulation of its oxygen-binding function. Other exceedingly important regulatory mechanisms of this function act at the cellular and molecular levels. They modify the functional state of the erythrocytes and of the hemoglobin. /240 These mechanisms help in regulating the processes of uptake and delivery of oxygen by the erythrocytes. The multiple regulations of the oxygen-binding function of the blood, at all three levels of organization of the erythron (systemic, cellular, and molecular), ensure high functional reliability of the erythrocytic system.

The regulation of the oxygen regime of the organism by the functional activity of the erythron can be represented as follows: A decrease in the pO_2 of the inspired air, or an increase of the tissue demand for oxygen under great physical stress, will reduce the partial oxygen pressure in the blood and lower its level there. This may trigger the physiological mechanisms that increase the oxygen capacity of the blood. This is accompanied by an increase in the oxygen content of the blood. The pCO_2 increases and the pO_2 decreases in the blood of the tissue capillaries, weakening the bond between hemoglobin and oxygen. Such functional reorganizations establish conditions under which the flow of oxygen from the erythrocytes into the cytoplasm increases at the instant at which the blood moves into the tissue capillaries. The sharpness of the drop in the pO_2 gradient between blood and tissues decreases, and the conditions of diffusion of oxygen from the capillaries into the tissues improve.

The ability of the erythron to control the oxygen capacity of the blood is responsible for its specific role in the general regulation of the oxygen regime of the organism. However, the role of the erythron in the regulation of the oxygen regime of the organism must not be regarded in its purely hematological aspects alone. An analysis of the functional capabilities of the streaming blood is also indispensable.

Such an approach permits an estimate of the result of the functional unit of erythron and blood circulation. In this case, we can speak not only of /241 the oxygen-binding but also of the oxygen-transporting function of the blood. The indices of the oxygen-transporting function of the blood are the maximum possible oxygen supply and the actual oxygen supply of a given minute volume of the streaming blood (MV).

The maximum oxygen supply of the MV is determined by its oxygen capacity. Such an index may be termed the oxygen-transport potential of the blood. The degree to which this potential is realized depends on the oxygenation of the blood in the pulmonary capillaries, i.e., on the degree of adaptation of the external respiration to the existing conditions of gas exchange.

The variation in the regulation of the oxygen regime as a whole requires consideration of the correlations between the indices of the functional activity of the oxygen transport system of the organism. A clarification of the regulatory processes involved in the optimum distribution of the functional load between these systems is of extreme interest.

Such an approach to the study of the processes of oxygen supply of the tissues, however, is not as widespread as it should be. Today, fragmentary studies of the functional shifts in the individual oxygen transport systems are

the dominant type. This is particularly true in hematological work. The revelation of the functional unit formed by the erythron with the blood circulation and the external respiratory apparatus will probably broaden our views on the physiology of the blood system itself.

There is no doubt as to the usefulness of studies on the combined action of the multifaceted process of adaptation to unfavorable conditions of gas exchange. Such an approach may also be valuable in the study of the functional development of the physiological systems during evolution of the individual /242 organism. For example, a study of the state of the oxygen-binding function of the blood in 2 week old puppies demonstrated that the mean oxygen capacity of their blood was considerably lower than in adult dogs. These values were 16.4 and 22.95 vol.%, respectively (determination in collaboration with M.M.Seredenko).

This is explained by the fact that, soon after birth, the erythrocyte count of puppies begins to drop sharply. At two weeks of age, the erythrocytic equilibrium is maintained at a lower level (3700 ± 470 thousand/mm^3) than in adult dogs (6656 ± 637 thousand/mm^3). However, because of the faster blood flow at this age, the oxygen-transport function of the blood is rather high in puppies, as indicated by the following data.

We found that the number of erythrocytes circulating per minute in the blood stream of these puppies is on the average 777×10^9 per kg of body weight, while in adult dogs it is 647×10^9 per kg of body weight. We also found that the oxygen-binding activity of the erythrocytes was higher in these puppies than in adult dogs. The mean oxygen capacity of one billion erythrocytes is 0.041 and 0.037 mℓ O_2, respectively.

Thus, despite the low erythrocyte count, the oxygen-transport potential of the blood (maximum oxygen supply in MV) in 2 week old puppies is higher than in grown dogs. In terms of body weight, these potentials are 31.8 and 23.9 mℓ /243 O_2/kg, respectively. The phenomenon of a decrease in the respiratory surface of the blood soon after birth, in human beings and most mammals, has been well established.

However, the fact of the decrease in the number of erythrocytes after birth, and the cause for the prolonged maintenance of erythrocyte equilibrium in the blood of the growing organism at a lower level than in the adults, have never found a generally recognized explanation. This question may perhaps be solved by a study of the functional interrelations between the erythron and the other systems.

In this respect, the following approach to the question may be suggested. The increased functional activity of the blood circulation during the development of the organism is physiologically normal. This is obviously necessary for satisfaction of the increased demand of the tissues of the growing organism for body-building and energy-building substances. With such an energetic circulation, the O_2-transport function of the blood is rather high so that the organism can get along with a smaller number of erythrocytes. As a result, the function of the erythroblastic system of the bone marrow becomes more economical.

There seems no justification for the assumption that the decreased erythrocyte level during this period of development is due to a functional insufficiency of erythropoiesis. No sufficient proofs for such an idea exist. The possibility of a synthetic approach to the study of the erythrocyte shifts in acute hypoxia can be demonstrated on the following example: In almost all our experimental dogs (15 out of 17), we found that the erythrocyte count increased in acute hypoxia. However, a true increase in the respiratory surface of /244 the blood was noted only in nine out of 15 animals. In the remaining six dogs, only the erythrocyte concentration in the blood varied, due to hemoconcentration (the plasma volume was determined by dilution with the dye T-1824). As a result, the total respiratory surface of the blood of these animals remained unchanged, so that there also was practically no change in the oxygen-binding function of the blood (Yu.V.Semenov, 1965).

However, if the factor of motion of the blood is taken into account, it will become clear that in connection with the hemoconcentration, each equivalent systolic volume of blood will have a larger oxygen supply, since it will have more erythrocytes. The oxygen-transport function of the blood will increase. Naturally, it must be taken into account that, if the volume of the circulating blood decreases (because of the plasma), an additional amount of energy will have to be expended on intensifying the contractile function of the myocardium to maintain the same cardiac output.

Thus, the analysis of the functional state of the blood in its statics and dynamics reveals the unity of the various aspects of its participation in the regulation of the oxygen regime of the organism.

CHANGES IN RESPIRATION, ARTERIAL PRESSURE, AND POLAROGRAPHIC INDICES IN HYPOXEMIA INDUCED BY MECHANICAL AND CHEMICAL ACTION ON THE BRAIN

/245

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This paper gives the results of three series of experiments. In the first series, the relative sensitivity of the respiratory and vasomotor centers to increased intracranial pressure, on perfusion of the ventricles of the brain, subdurally and in the spinal cord, was studied on 50 cats under urethane narcosis (1 gm/kg). The pressure was varied from zero to 315 cm H_2O. The following patterns were found:

An increased pressure in the liquid perfused through the ventricles of the brain, or into the spinal cord, by 15 - 20 cm H_2O does not change the respiration; in rare cases it increases the arterial pressure. The same increase in the pressure between the dura mater and the pia mater increases the arterial pressure but does not change the respiration.

Regular reactions of the arterial pressure begin to be observed at pressure increases of 25 - 30 cm H_2O in the ventricles of the brain, in the spinal cord, and beneath the dura. Respiratory reactions, however, are regularly observed only at a greater pressure rise (by 35 - 40 cm H_2O).

It follows that the vasomotor center is more sensitive than the respiratory center to direct mechanical stimulation.

At greater increases in pressure, the character of the respiratory re- /246
actions depends largely on the ability of the intravascular pressure to overcome the increasing external pressure on the bloodvessels of the brain (into the cavities of the ventricles, spinal cord, and subdural space) at low arterial pressure, i.e., when there is no compensation for the increased external pressure, or when such compensation is inadequate, respiration may become pathological or stop entirely, even at the relatively low excess pressure on the brain of 105 cm H_2O; conversely, at pronounced functional mobility of the cardiovascular system, respiration may be maintained even at a pressure of 315 cm H_2O on the brain or more.

In the second series, we performed 22 experiments on dogs (narcosis was obtained with 1 ml of a 10% sodium diapental solution for 3 kg of body weight). In each experiment, 2 - 7 observations were made. A device for compressing the medulla oblongata was introduced through a trephined opening between the base of the skull and the medulla oblongata. The results, except for minor differences, more or less confirmed the data of the first series. The qualities of the cardiovascular reaction were the same. In the great majority of the cases, in response to the increased pressure on the brain, the cardiac rate was reduced, at a brief drop in arterial pressure (like that taking place on increas-

ing the pressure in the isolated carotid sinus). Thus, in reflex action through the vascular pressure receptors as well as with increased pressure on the brain, a reaction of the same type occurs initially, namely, a drop in arterial pressure. Later, the increasing pressure on the medulla oblongata /247 causes an increase in arterial pressure, to an extent depending on the functional mobility of the cardiovascular system and on the degree of pressure on the brain. If the animal does not die after the increased pressure on the brain has stopped, the arterial pressure remains high for 2 min or longer, after which it gradually, like the heart rate, returns to its original level. Generally, respiration is first accelerated but then retarded and deepened (in the manifestations in cats, inspiratory, and in dogs expiratory) with apnea of various pathological types and irreversible respiratory arrest. After interruption of the anemia, frequent, rapid, and shallow respiration generally sets in. If respiration is present, normal respiration will be restored already during the first minute. However, if there was no respiration before elimination of anemia, stoppage of the anemia is usually followed by an initial drop in arterial pressure and a subsequent rise; often, at the height of this rise the respiration is restored. During the disturbance of respiration and arterial pressure, the oxygen tension in the tissues of the medulla oblongata decreases sharply.

In the third series (30 cats; narcosis hexenal, 0.03 - 0.04 gm per kg of body weight), we studied the respiration and oxygen tension in various regions of the medulla oblongata and in the fissure of Sylvius of the cerebral cortex under the action of adrenaline (0.35 - 0.5 ml of 0.1% solution) and noradrenaline (0.05 and 0.3 ml of 0.2% solution), injected into the peripheral end of the carotid artery. We found that the oxygen tension in the cerebral cortex /248 and in various regions of the medulla oblongata does not always vary in a parallel manner, nor qualitatively in the same way, on inhibition of respiration by these drugs.

It follows that the vasomotor center is more sensitive and more resistant to variations in intracranial pressure (anemia) than the respiratory center.

THE ROLE OF EXTERNAL RESPIRATION IN THE REGULATION OF THE OXYGEN REGIME OF THE ORGANISM

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The function of the external respiration is primarily concerned with maintaining a constant level of the pO_2 and qO_2 of the alveolar air and the arterial blood, i.e., the parameters at the output of the first and second stages of the oxygen regime control system (ORCS), the lung reservoir, and the reservoir of the pulmonary capillaries.

A calculation of the amount of oxygen and its tension at the input and output of these stages permits: 1) characterization of the oxygen regime and 2) definition of the role of the external respiration in the control of the oxygen regime (OR), depending on various conditions.

To characterize the level of the OR in the first stage, based on data obtained by us in collaboration with A.Z.Kolchinskaya, N.V.Lauer, N.T.Khilinskaya, and M.A.Kulikov, the following amounts of oxygen were taken: arriving per minute from the atmosphere (q_1O_2), arriving per minute in the cavity of the alveoli (q_AO_2) and leaving the alveolar air per minute into the blood, i.e., practically speaking, the oxygen consumption per minute (q_tO_2). In the graphic representation of these quantities in the form of a step diagram for persons age 6, 16, 29, and 70 years, under the conditions of rest and at normal pO_2 in the inspired air, we found that the level of the OR in this stage is lowest in the child, higher in the youth, and highest in the adult. In the old person, the level of the OR is peculiar: the q_1O_2 is higher than in the other age periods, while in the succeeding stages the OR level declines and approaches that of youth. However, if the oxygen arrival per minute from the atmosphere is calculated per kg of body weight, we find that for a 29 year old human subject it is lowest of all. It is somewhat higher at age 16, still higher in the old person, and highest of all in the 6 year old child. The q_AO_2/kg is higher in the adult than in the old person or in the youth, ensuring a relatively high level of the q_tO_2/kg at this age. In the child, the entire O_2 cascade is of considerably higher intensity than in the other age groups, but the gradients between the stages of the cascade are far greater in magnitude.

/250

Our data permit an approach to evaluating the effectiveness of the OR, which may be represented by the ratio of the quantity of oxygen passing through the stage of the ORCS to the oxygen consumed, and also between the stages. For the first stage, these ratios are q_1O_2/q_tO_2; q_AO_2/q_tO_2; and q_1O_2/q_AO_2. These ratios are lowest in the adult, permitting us to speak of a maximum effectiveness of OR in this age. In youth, the effectiveness of the OR is less, being still lower in the child, and lowest in old age.

The gradients of pO_2 at the input and output of the first two stages yield data on the conditions under which oxygen exchange takes place in the pulmonary reservoir and in the blood of the lung capillaries. In the various age periods, the gradient between p_AO_2 and p_aO_2 fluctuates. The fact that this gradient is greatest in old age and smallest in the adult may indicate that /251 the stress of the OR is greatest in this stage in old age and lowest in this stage in middle age.

The oxygen regime of the organism in the first stage may also be used for estimating its economy, as indicated by the ratio of the indices of external respiration and oxygen consumption. These ratios also assist in characterizing this function of the organism.

One of such relations is the ventilation equivalent, which is the ratio of the minute volume (MV) of respiration to the q_tO_2, which yields the volume of air passing through the lungs required to supply the organism with 1 $m\ell$ of O_2. It is highest in the old person, somewhat lower in the child, substantially lower in the young person, and lowest in the adult. This alone would indicate that the oxygen regime in the first stage is most economical in middle age and least economical in old age.

This can be demonstrated also on the basis of another index, namely, the ratio of alveolar ventilation (AV) to q_tO_2, which yields the volume of air that must enter the alveolar part of the lung for 1 $m\ell$ of oxygen consumption. In fact, the smallest volume of air is required for this in middle age and youth and the largest in childhood and old age.

In this same connection, there is a third index of the OR economy in this stage, which might be of interest. This index yields the amount of oxygen consumed by the organism, from the air delivered to the lung in one respiratory cycle. The greatest amount of O_2 is consumed in middle age, considerably less in old age and youth, and very little in childhood. /252

These data permit the general conclusion that the function of the external respiration of the organism in a state of rest and at normal pO_2 of the inspired air, is most economically performed in middle age. This function is less economical in youth and least economical in childhood and old age.

It is of interest that if, at constant tissue oxygen consumption, the ratios of the functional indices of external respiration to the oxygen consumption were the same in childhood and old age as in middle age, then some of the indices at these ages would have the following form: The MV in the child would be only 2.5 ltr instead of 4.0 ltr; in the person of 70 years of age, it would be 4.8 ltr instead of 8.4 ltr. The alveolar ventilation in the child would be 2.1 ltr instead of 2.9 ltr; in the old person it would be only 3.9 ltr instead of 4.9 ltr. The respiratory rate would be only 3 per min instead of 22 per min in the child, and in the old person only 6 per min instead of 16 per min.

Hence, it is clear that, at the economy of the OR in the first stage inherent to middle age, some indices of external respiration in childhood and old age would be considerably lower. In old age and childhood, however, such economy of the external respiration would lead to extensive impairment of the regulation

of the oxygen parameters.

An overall evaluation of the oxygen regime, and in the first stage of the ORCS in particular, using a hypoxic model, is complicated by the fact that the above indices of the OR are characteristic for a regime in the stationary state, while in acute hypoxic hypoxia the oxygen exchange in the organism takes /253 place under the conditions of a transitional regime. Thus, an evaluation of the OR in acute hypoxia constitutes only a tentative approach to this question.

At inhalation of gas mixtures with lower pO_2 and qO_2 (with a drop from mixture to mixture, corresponding to an altitude increase of 1000 m) for dogs of moderate age at relative rest, N.V.Lauer, A.Z.Kolchinskaya, the present authors, M.M.Kaganovskiy, V.V.Turanov, and N.T.Khilinskaya have noted the following:

Down to mixtures with 12.7% O_2 (corresponding to an altitude of 4000 m), the intensification of the function of external respiration, expressed in an increase of the MV, more or less maintains the initial level of the q_1O_2 and to a lesser degree that of the q_AO_2. Due to this fact, the level of the OR in the first stage on these mixtures varies only slightly (mainly on account of an increase in q_tO_2). At 11.0% O_2 (5000 m) we note a decline in the level of the OR at all stages, with a substantial decrease in q_tO_2 despite the continuing increase in MV. From the viewpoint of OR efficiency, it is an interesting fact that the ratios q_1O_2/q_tO_2 and q_AO_2/q_tO_2 continue to decrease on transition to each new mixture, down to 12.7% O_2, where they stabilize with a sharp increase for the mixtures with 7.5% O_2 (8000 m); finally, in characterizing the economy of the OR in the first stage and in evaluating the function of external respiration from this viewpoint, one should note the slight increase in the ratio of MV/q_tO_2 down to the mixture with 12.7% O_2, followed by its sharper increase /254 and considerable rise at 7.5% O_2. The ratio AV/q_tO_2 also fluctuates about its initial level down to 12.7% O_2 and then repeats the variation of MV/q_tO_2, although to a lesser degree. The ratio q_tO_2/RR (where RR is the respiratory rate) likewise increases down to the mixture with 12.7% O_2, and then gradually decreases to 7.5% O_2, where it drops sharply.

An analysis of the data obtained for dogs of medium age shows that the intensification of the function of external respiration under conditions of acute hypoxia is rather effective and economical up to an altitude of 4000 m (mixture with 12.7% O_2), and, despite the progressive decrease in pO_2 and qO_2 in the inspired air, ensures the level of q_tO_2 necessary for the organism. A decline in the effectiveness and economy of this function is noted at still more severe hypoxia; above altitudes of 8000 m, there is a substantial incoordination in the variations of the functional indices, leading to extensive disturbances of the oxygen regime of the organism.

These propositions, characterizing the oxygen regime of the organism, make no claim as to complete elucidation of the question and are merely advanced to attempt a fuller and more comprehensive understanding of the oxygen exchange in the organism during its first stages under various conditions (age and hypoxia) as well as to evaluate the role of the system of external respiration in oxygen exchange.

THE EFFECT OF ACUTE HYPOXIA OF THE BRAIN ON THE FUNCTIONAL STATE OF THE CARDIOVASCULAR SYSTEM

/255

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The effect of isolated acute hypoxia of the brain on the circulation was studied in dogs. The hypoxia was induced by veno-arterial craniocerebral perfusion, using artificial circulation apparatus. In eight of the 19 experiments, the venous blood, arriving in the apparatus from the right heart of the animal, was first saturated with nitrogen to prevent hypercapnia of the brain. In the experiments, we measured the electric activity of the cerebral cortex, the biocurrents of the heart, and the arterial pressure and studied the blood gases, the indices of the acid-base equilibrium, etc. The volume rate of flow of perfusion varied from 5 to 20 mℓ per kg of body weight, and hypoxia of the brain was developed in varying periods (from 20 to 80 min). A two-phase change in the biocurrents was noted on the EEG, first showing in an acceleration of the rhythm followed by dominance of slow waves. The development of hypoxia was accompanied by a rise in the arteriovenous oxygen difference (A - Vp_{O_2}).

The A - Vp_{O_2} of the blood, forced into the carotid artery and flowing over into the internal jugular vein, increased from 33.5% to 43% in the experiments without nitrogen (average of 11 experiments). At the same time, the A - Vp_{O_2} /256 in the blood samples from the femoral artery and femoral vein increased from 27 to 48% (average values), while the pCO_2 in the forced blood in each group was 42 mm Hg on the average.

When the venous blood was saturated with nitrogen, the mean pCO_2 was 33 mm Hg in eight experiments. The A - Vp_{O_2} also increased in this group with the development of hypoxia, but to a lesser extent, namely, from 20 to 24% (average of eight experiments). The A - Vp_{O_2} in the blood samples from the systemic blood vessels increased from 30 to 35.4%.

In all of the experiments, the increase in hypoxia of the brain was accompanied by disturbances in the hemodynamics. The arterial pressure fell to 40 - 20 mm Hg. Resistography of the blood vessels of the hind leg, in four experiments, showed relatively resistant vasotonia. The sharp drop in blood pressure and the developing oxygen insufficiency of the organism are results of reflex disorders of the cardiac activity. This was evidenced by the changes in the ECG. We noted acceleration of the heart rate to severe tachycardia (90 - 220 per min) and a decrease in the voltage of the ECG waves. In the experiments with nitrogen saturation of the blood, these changes were somewhat less pronounced.

DYNAMICS OF RESPIRATION IN ATHLETES UNDER CONDITIONS OF HYPOXIC HYPOXIA

/257

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Dynamics of respiration encompasses the processes keeping the air in motion through the respiratory passages. The elastic and inelastic elements of the thorax participate directly in these processes, which is also true for the air stream in the tracheobronchial tree offering a certain resistance to respiration.

In young healthy subjects, the first two of these factors cannot restrict the functional capability of the external respiration system. The resistance of the respiratory passages in the state of rest likewise has no limiting effect here. However, since it is proportional to the square of the velocity of the air stream, the resistance may increase under certain conditions. A physical stress is one of these.

In the untrained person, even a relatively low stress, not requiring an excessive increase in pulmonary ventilation, is accompanied by the sensation of difficult breathing: dyspnea. Yet athletes, under great physical stress, and with the pulmonary ventilation rising to 100 ltr/min and higher, experience no difficulty. This is evidently explained by the high level of the regulation achieved during athletic training.

There are various methods of investigating the resistance of the respiratory processes. First, it can be determined by the power of the air stream /258 in forced inhalation and exhalation, by the Tifno test, the vital capacity, etc.

There is a connection between the resistance of the respiratory processes and the bioelectric activity of the respiratory musculature. In breathing against an artificially increased resistance, the activity of the respiratory muscles increases sharply, in spite of the decrease in the ventilation volume (Keene and Otis, In' Chi-Chang, A.M.Kulik and others). Campbell and Green found a correlation between the activity of the respiratory musculature and the intrathoracic pressure.

Many authors believe that nervous regulation is involved in this phenomenon, especially the vagus nerve (B.A.Botvinnikov, I.Sh.Ginzburg, and others, L.I.Shik, Fleisch, and others). The state of excitability of the respiratory center, determined by its afferentation, plays an important part (M.Ye.Marshak).

On inhalation of a low-oxygen gas mixture, there is a reflex increase in the tonus of the respiratory passages, owing to the excitation of the chemoreceptors of the sinocarotid zone.

In this case, the total resistance of the lungs increases, while the volume of the trachea decreases. In the opinion of Neidler and Widdicombe, under normal conditions the tonus of the respiratory passages, due to various nervous influences, maintains the optimum relation between the resistance to respiration and the dead space.

Our own investigations, in collaboration with V.V.Matov at the Sports Medicine Sector of the above Institute for Physical Culture, have shown that in hypoxic hypoxia in the altitude chamber, changes occur in the dynamics of /259 respiration, even in the state of rest. Our subjects, who were highly trained athletes, swimmers, and medium-distance runners, were examined both under basal conditions and at the simulated altitude of 5000 m.

We synchronously registered the bioelectric activity of the inspiratory (intercostal) and expiratory (musculus obliquus externus abdominis) muscles, a mechanogram of the respiratory movements of the thorax (by pneumography), and a spirogram on an N-700 loop oscillograph.

We studied the components of the electromyogram of the respiratory musculature, the duration of the phases of the respiratory cycle, the rate, depth, and minute volume of respiration, and the volumetric rate of expiration.

The changes in respiration dynamics during hypoxic hypoxia are proved by: the substantial increase in the bioelectric activity of the inspiratory muscles, which was particularly distinct when expressed per liter of ventilated air, observed after a 30-min stay at a simulated altitude of 5000 m; the decrease in the minute volume and depth of respiration; the considerable lengthening of the duration of exhalation; and the decrease in excursion of respiration.

There are reasons for assuming that these changes might limit the fitness and performance of athletes under such conditions.

OXYGEN SUPPLY OF THE ORGANISM IN ANEMIC AND CIRCULATORY HYPOXIA UNDER HIGH-MOUNTAIN CONDITIONS*

/260

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Our studies were performed on animals with induced heart defect (destruction of the aortic valves by valvotomy) and on dogs after blood loss of 2.5% of their body weight. The observations were performed in the city of Frunze (altitude 650 m) and in the village of Tyuya-Ashu (altitude 3400 m).

Together with the circulatory function, we also investigated the oxygen budget of the organism, in an attempt to discover the nature of the compensatory mechanisms in circulatory disturbances and in acute blood loss under high-mountain conditions.

In all, 67 animals were used in the experiment. Of these, 21 dogs were examined at Frunze and 46 at an elevation of 3400 m. Some of the animals (unacclimated) were used in the experiments 3 - 5 days after their arrival in the high mountains, and others after staying a month at the same altitude.

The control group (healthy dogs), after their transfer to the high mountains, showed an increase in respiratory metabolism and variations in blood oxygenation. The oxygen consumption increased to 88 ml/min, compared with the initial value of 69 ml/min at Frunze, and the minute volume (MV) increased by about the same amount. The pulse was also accelerated. The oxygen saturation of the arterial blood declined to 82% from an initial 98%, and that of the venous blood to /261
54% from the 58% at Frunze.

About 12 - 14 days after arrival at the high-altitude localities, the MV still remained high, the oxygenation of the venous blood reached 55%, and the other indices showed a distinct tendency to normalization. By the end of the month, the oxygen uptake differed little from the initial values at Frunze. A regular rise in the hemoglobin content was noted (11.3%).

The animals with the induced heart defects also compensated the oxygen insufficiency in the external air by increased respiratory metabolism and by changes in the circulatory function. These changes, however, were more pronounced than in the healthy animals. After transfer of the animals to the high level, they developed severe tachycardia and polypnea. The blood flow slowed, and the oxygenation of both arterial and venous blood declined (by 6.6 and 12.3%, respectively). The oxygen uptake increased by 28%. Despite the fact that, in

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* Based on experimental material of the author and his associates: Assistant A.K.Kadyraliyev and postgraduate student Ye.M.Yefimova.

percentage, the respiratory metabolism increased almost as much as in the healthy animals, the oxygen uptake had not yet reached the initial levels at Frunze, after a full month at the high elevation.

Thus, while the healthy animals reached a certain degree of acclimation by the 30th day of their stay at the high level, the animals with valvular heart defect still had not developed sufficient adaptation to the low oxygen content of the surrounding medium.

In these animals, however, under the high-mountain conditions, the heart muscle developed a degree of hyperfunction sufficient to maintain not only /262 the function of the circulatory system but also to supply the tissues with oxygen, to an extent approximately corresponding to the severity of the pathological processes under the conditions at Frunze.

The animals subjected to blood loss exhibited more severe disturbances of circulation and respiratory metabolism after a drop in barometric pressure. In our previous studies, we had demonstrated the regular difference in the respiratory functions of the blood during the first two hours after anemization and in the following days, when acute posthemorrhagic anemia developed. A similar phasicity of the pathological process persisted even under high-mountain conditions. On the mountain pass of Tyuya-Ashu, at the same degree of anemization, the unacclimated animals showed more severe tachycardia during the first two days than at Frunze (214 beats/min against 179 for the controls). The slowing of the blood stream reached an extreme degree (13.4 sec against 11 sec for the control), and the arterial pressure fell to lower values than at Frunze (by 60% instead of 38% in the controls). The hypothesis may be advanced that, under high-mountain conditions, regulation of vasotonia is impeded, since the animals are unable to properly mobilize their compensatory reserves. It is striking that, in the dogs, the minute volume at the high elevation increased by a smaller amount (18.9%) than at Frunze (26.7%). The respiratory metabolism varied similarly, i.e., the oxygen uptake decreased.

However, 2 - 3 days after the blood loss, the unacclimated animals, as at Frunze, exhibited an increase in respiratory metabolism and even a certain increase in the oxygen utilization factor. The cardiac output also increased, /263 as it did at Frunze, but this compensatory mechanism was less pronounced (especially after 24 hrs).

Consequently, in the unacclimated animals at 3400 m elevation, the initial period after the blood loss shows a severe deterioration, with more pronounced changes in the circulation than usual taking place. In some cases, the animals died from acute circulatory hypoxia. The second period, with manifestations of anemia, was characterized by some restoration of hemodynamics, but the oxygen supply of the organism did not reach the level observed after the anemization at Frunze. The healthy animals, after staying a full month at 3400 m elevation, still showed a certain increase in the volume of circulating blood at the end of the month, while the cardiac output was elevated and the oxygen uptake also was higher (10 ml instead of the initial 7.5 ml O_2/kg body weight/min). There is an appreciable decrease in the oxygenation of the arterial and venous blood. Apparently, during the 30-day period, only the "unstable phase of acclimation" (M.M.Mirrakhimov) sets in, and becomes especially distinct when the animal is

subjected to greater stress. Thus, during the first two hours after a blood loss equal to 2.5% of body weight, the arterial pressure drops by 54% (at Frunze, it dropped only 38 - 40%), and the cardiac output decreases by 28.7%. The amount of absorbed oxygen begins to decline and - what is most important - the decrease in respiratory metabolism continues even in the days following the bloodletting. Ultimately, however (after 5 days), the oxygen uptake was at about the same level as at Frunze (113 ml instead of 116 ml O_2/min). After one month in the mountains, the animals responded to the blood loss in the phase of development/264 of anemia by satisfactory compensation of the circulatory system: The cardiac output increased by 0.7 ltr over the initial level, and the blood flow accelerated. However, these adaptive shifts were unable to provide normal oxygenation of the arterial and venous blood. The oxygen saturation of the blood decreased to 81 and 45%, respectively.

To summarize our studies on the nature of the oxygen budget in valvular heart defects, and in animals after bloodletting, it must be concluded that the dogs, under the conditions of high-mountain hypoxia, are quite readily able to intensify the function of their circulatory system; this, together with a reorganization of the other functional systems, ensures a relatively good oxygen supply for the organism and provides for adequate adaptation to the reduced partial oxygen pressure.

Of course, one month in mountain localities at 3200 - 3400 m elevation is insufficient for complete acclimation to the conditions of hypoxic hypoxia, a fact which is particularly noticeable in cases where the compensatory mechanisms of the animal are subject to higher demands.

The processes of complete acclimation to high-mountain hypoxia are slow in becoming established and evidently take longer to complete.

THE EFFECT OF PROTRACTED EXPOSURE TO A HYPEROXIC MEDIUM ON THE HIGHER NERVOUS ACTIVITY OF ANIMALS

/265

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The scanty literature data as to the effect of a hyperoxic medium on the higher nervous activity were mostly obtained in short-time exposures.

The object of the present work was to investigate the higher nervous activity of animals under the protracted action of a gas mixture with increased oxygen content.

White male mice (of strain CC 57) aged 3 months were used. The experiments were performed in a special chamber in which a prescribed oxygen concentration was maintained. The control group of animals was kept in a similar chamber filled with atmospheric air.

The state of the higher nervous activity of the animals in the different media was evaluated from the rate of development of conditioned defense reflexes, in a modified Aleksandrov-Tsibina apparatus.

We found that a stay in a medium containing 40% oxygen had no substantial effect on the development of conditioned reflexes in mice. When the animals were exposed to a medium with 60% oxygen, the development of conditioned reflexes was somewhat delayed. In a hyperoxic medium, with 80% oxygen, the /266
formation of conditioned reflexes lagged sharply. A medium with 90% oxygen completely inhibited any conditioned-reflex activity, exerted a clearly toxic action on the organism, and resulted in death.

The possibility of formation of conditioned reflexes to a hyperoxic medium was considered as one of the aspects of the adaptation of animals to this factor. The rate at which conditioned reflexes are formed is a sufficiently sensitive test for evaluating the influence of a hyperoxic medium on the functions of the central nervous system.

MAXIMUM OXYGEN CONSUMPTION, AS AN INDEX OF THE EXTENT OF OXIDATIVE PROCESSES AND OF GENERAL PHYSICAL FITNESS

/267

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The individual features of the respiratory function of man are characterized primarily by two factors: oxygen consumption under conditions of the basal metabolism, and maximum oxygen consumption (MOC) under conditions of strenous muscular work. The former characterizes the lower normal limit for the oxidative processes that maintain the vitally necessary functions of the organism at muscular rest and at normal state of the external medium. This quantity depends on the mass and size of the body, as well as on age and sex. Its magnitude varies when the activity of certain endocrine functions is disturbed under the influence of conditioned reflexes that signal the onset of strenous muscular work or of temperature changes. It may reflect a state of heavy muscular work that has just passed, but is only slightly responsive to a greatly changed level of training. The basal metabolic rate does not constitute a reliable index for the general physical fitness and state of training of a given individual.

The second quantity characterizes the upper limit of the oxidative processes for a given organism, i.e., the level of extremely strenous and active muscular work. It depends on the active mass of the body, varies little under the /268
influence of moderate external stimuli, and distinctly reflects the general physical fitness and the level of training.

A necessary condition for determining the MOC is the willingness of the subject to go to the limit of his strength. The work performed must not be done at maximum exertion, since work at this level can be done only over anaerobic processes in the muscles, produces no substantial increase in oxygen consumption, and can be continued for only a short time (10 - 20 sec). Work done with the object of intensifying the oxidative processes in the human body to the extreme limit, must proceed at a power output in the zone of "submaximum" or "great" relative power and must continue for one, or several, minutes. It should be preceded by an "unlimbering" period, in the form of exercise at gradually increasing power, in order to fully mobilize all mechanisms for oxygen transport and uptake. The several versions are conditions for determining MOC, but the differences between them are not fundamental.

The MOC is determined by the interaction of a number of factors: partial oxygen pressure in the inspired air, volume of lung ventilation, respiratory surface of the lungs, diffusion of gases between lungs and blood, oxygen capacity of the blood, hemoglobin level, acidity of the blood and its alkaline reserve, volume rate of flow of the blood, degree of local blood supply to the lungs and working muscles, activity of the oxidizing ferments in the tissues, arteriovenous difference, degree of blood oxygenation in the lesser circulation, etc. Even this short list is sufficient to show that the MOC is an integral criterion for

the degree of perfection of the functioning of the various systems of the organism. It must be added that, to ensure maximum oxygen consumption, a high degree of mutual adjustment of the interaction between the various physiological symptoms is required, all of which must function at the very peak of their ability. Of particular importance here is the ejecting power of the heart, i.e., the maximum possible ejection of blood by the left ventricle, which most authors regard as the rate-determining factor of the MOC. /269

The highest values of MOC obtained to date are 5.8 - 6.2 ltr/min (85-90 mℓ per kg of body weight). For the organism to be able to utilize such an amount of oxygen, the following conditions must be met: minute volume of respiration 120 - 200 ltr/min; cardiac output 33 - 35 ltr/min; oxygen saturation of arterial blood not less than 92 - 93%, and arteriovenous oxygen difference 14 - 16 vol.%. It is absolutely clear that such values of the respiratory and cardiac outputs are entirely impermissible for an untrained organism; such levels require long years of systematic athletic training, during which phenomenal morphophysiological reorganizations take place in the various functional systems.

Not every type of athletic training, however, has the same effect in encouraging an increase in the MOC. Exercises with pronounced speed and force components do increase the capability of the organism for extreme consumption of O_2 but only by a relatively small amount; for this reason, the MOC of high-jumpers, gymnasts, football players, and sprinters does not exceed 50 - 60 mℓ/kg. The highest MOC are found in athletes who have been trained primarily for endurance (skiers, long-distance and marathon runners).

The maximum values of oxygen consumption during muscular work limit the overall working capability of the organism, a point manifested with particular distinctness in athletics, especially in forms involving prolonged cyclic efforts lasting over one hour, and where the liberation of energy proceeds predominantly under the conditions of free oxidation. Many years of MOC determination among top athletes have shown that the major events are as a rule won by persons with an MOC of 75 - 85 mℓ/kg; specialists in the field have established the great prognostic value of this test. /270

CONTRIBUTION TO THE QUESTION OF THE COMPENSATORY REACTIONS OF THE ORGANISM UNDER CONDITIONS OF HYPOXIA AND ACCLIMATIZATION

/271

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The problem of oxygen insufficiency, despite the progress made in some areas, remains topical even today, since oxygen want is encountered in many diseases as well as on ascents to high altitudes.

It is well known that the organism has a large number of compensatory mechanisms that can be utilized under the conditions of oxygen want. The particular compensatory mechanism put into operation is dictated by the degree of hypoxia (if we are discussing the altitude chamber) or by the combined influence of climatic factors.

In this connection, a study of the compensatory mechanisms in various forms of hypoxia is one of the most urgent problems.

In our investigations, which were performed over a span of many years by a large group of coworkers (A.D.Taranukhina, N.F.Pisarenko, I.A.Fantalis, I.Ya. Bliznetsov, E.Z.Abdikasheva, and others), we succeeded in establishing a number of laws for the physiological functions in acute oxygen want (in the altitude chamber) and acclimatization in Kirgizia. Up to an elevation of 2500 - 3000 m, acclimatization in Kirgizia is characterized by a pronounced decrease in the /272 energy expenditures of both humans and animals, especially in the summer. The decline in the basal metabolism favors a decrease in pulse rate, blood pressure, and amount of enzymatic elements in the blood.

However, in a large number of different species of animals (yellow squirrels, gray hamsters, white rats, guinea pigs, muskrats, rabbits, etc.) we have found, under conditions of acute hypoxia, that "altitude" stimulates the respiratory metabolism and the respiratory function of the blood, and that a high "ceiling" is encountered here. However, if these animals are bled (up to a 50% loss of erythrocytes and blood hemoglobin), the "ceiling" is still maintained, except that here this is no longer effected by stimulation of the respiratory metabolism and respiratory function of the blood but by a considerable decrease in the energy expenditure.

Evidently, the organism, in reacting to oxygen deficiency, activates the compensatory mechanisms that are most suitable for protecting it from hypoxia at a given instant. If, for some reason, one of the mechanisms fails, the organism is able to switch to others acting at the given instant. Such a decrease in energy expenditure of the organism occurs during inhibited respiration in hibernating animals or in hedgehogs when they coil up at a time of danger. The lowering of the energy exchange in this case is a reflex, as indicated by the rapidity of the reaction. For example, the metabolism of the hedgehog may drop

by 40 - 50% within a few minutes.

In our studies, we also established that the raising of the "ceiling" on decerebration is largely connected with a decrease in metabolism and a lowering in body temperature of the animal (experiments on pigeons). When various /273 exteroceptors of the animal are disconnected, the "ceiling" constantly rises against the background of lowered energy expenditure.

All this speaks in favor of the assumption that the decrease in energy expenditure is one of the leading mechanisms in adaptation to hypoxic states.

Under the conditions at Kirgizia, we observed seasonal variations in the fundamental physiological functions in both man and animal and also established a seasonal variation in the energy exchange. Against the background of a decreased metabolism throughout the year, the lowest energy exchange was observed in summer, i.e., in the period of the highest ambient temperatures. The lowering in metabolism did not lead to manifestation of reflex reactions such as the specific-dynamic action of eating or the daily periodicity of the principal vital processes of the organism (diurnal fluctuations in energy exchange, body temperature, etc.).

However, on determining the oxygen shortage in the organism with bloodless methods (according to Ulenbrook, 1930, where the principle of the method makes use of the fact that a healthy subject at rest does not change his oxygen uptake when the oxygen content of the inspired air increases), we encountered insufficient oxygen supply in healthy subjects. In this case, the oxyhemograph did not show as pronounced an arterial hypoxia.

A clarification of the cause of insufficient oxygen supply is the subject of our future research.

CONTROL OF TISSUE EXCHANGE, AND ITS VARIATION WITH AGE /274

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1. An accurate concept on the adequacy of the level of oxygen exchange with reference to the "needs" of the tissues can be obtained from defining the correlations between structure and functions of the cells and their energy supply.

One of the basic problems of the near future should be to establish the distribution of energy expenditure over various functional and growth processes in cells. With increasing age, there does not occur a simple quantitative variation in oxygen consumption but rather a redistribution of oxygen utilization over the various requirements of the cell. Under the conditions of stressed activity, this will lead to "struggle" for the energy resources of the cell, which is particularly acute in the aging organism.

2. The senile changes in oxygen exchange in the tissues are largely determined by two opposing tendencies: on the one hand, adaptation to the changing oxygen supply and, on the other hand, deterioration of the adaptive mechanisms, largely due to senile changes during renewal of the various members of the system of tissue respiration.

3. The mechanisms of the variation in the oxygen exchange within the tissues may be discovered by defining the correlations of the individual members of the complex controllable system, including oxygen, enzymatic systems, oxidation substrates, accumulated metabolites, and the complex group of neurohumoral effects.

4. The decrease in oxygen consumption in the aging organism is explained /275 both by the decline in the number of mitochondria and by the decrease in their oxidative activity. The latter is connected with the change in the correlations between activity of the respiratory enzymes (coenzyme A, succinic oxidase system, cytochrome system of cytochromoxidase), and the quantity and quality of oxidation substrates. The change in the diffusion of oxygen across a membrane and the decrease in the quantity of myoglobin are of prime importance.

5. In the system of oxygen supply to the tissues in old age, the feedbacks realized by the accumulation of a number of metabolites (ADP, NP) are subject to stresses. This leads to changes in the interrelation between oxidation and glycolysis in the cell. The feedbacks largely determine the interrelation between the oxygen exchange and the energy expenditure of the cells. The author compares the evolutionary differences in the metabolites, "including" feedbacks on the level of external and tissue respiration.

6. In evaluating the oxygen exchange in the tissues, one must distinguish between the potential and actual activity of the respiratory enzymes. The potential capability of the enzymes declines with age, which has a particular effect on the functions of the tissues under conditions of their intense activity.

7. At progressing age, the tissues develop adaptation to the change in the level of their oxygen supply, causing a narrowing of the range of variation of tissue respiration at various partial oxygen pressures.

8. Neurohumoral influences control both the consumption of oxygen in the tissues and its further utilization. The pathways of this influence differ: /276 variations in the activity of individual enzymes, shifts in the correlation between oxidation and phosphorylation, influence on the energy input and output of the cell, cut-in of the feedbacks, etc. The change, with age, in the sensitivity of the tissues to nervous and humoral influences affects the processes of oxygen exchange.

9. The neurohumoral regulation of the cardiovascular and respiratory systems also changes with age. Due to this fact, any change in the requirements of the tissues will lead to less pronounced but more protracted changes in hemodynamics and respiration under the conditions of hypoxia.

10. The mechanisms of adaptation of the "servosystems" to the requirements of oxygen exchange in the tissues are largely determined by the tissue chemoreceptors. With age, the sensitivity of the chemoreceptors to hypoxic factors increases. This increase of sensitivity, at the feedback stage, in the regulatory system for the hemodynamic supply of the tissues, may somewhat compensate the shifts in the direct neurohumoral influences.

11. The changes with age, in the tissue oxygen exchange and in the sensitivity of the bloodvessels to nervous and humoral influences are decisive for the changes in hemodynamics of the tissues under the conditions of their growing need for oxygen.

12. The mobilization of the feedbacks and the extensive utilization of the adaptive mechanisms to a deficit in oxygen supply of the tissue makes them - in senescence - particularly "vulnerable" to inadequate blood supply. This is responsible for many of the features of various pathological processes.

13. With age, it is not so much a question of a simple extinction but /277 rather of a complex irregular change of the adaptive mechanisms in the regulatory system for the oxygen exchange in the organism.

QUANTITATIVE CHARACTERISTICS OF WORKING HYPEREMIA OF THE SKELETAL MUSCLE AND THE CONCEPT OF THE BLOOD DEBT

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1. Ever since it was first demonstrated that the skeletal muscle uses more oxygen, not only during contraction but even for a long time thereafter, this phenomenon has been termed "oxygen debt". Long after relaxation, the blood supply of a muscle remains at a high level; this phenomenon, in analogy to the oxygen debt, is considered the payment of the debt, the "blood debt", formed during work. In this paper, we discuss this idea on the basis of data obtained in collaboration with L.A.Manvelyan and V.A.Khorunzhiy in a study of the mechanism of functional hyperemia. The motor fibers of the sciatic nerve in the cat were stimulated by impulses of varying frequency or amplitude, under variation of the pattern and duration of the contractions of the gastrocnemius; we measured the force of contraction (or shortening) of the muscle, the blood flow at the time of maximum dilatation of the blood vessels, the total blood supply during the period of contraction, and the period of recovery.

2. Both the degree of dilatation of the blood vessels of the contracting muscle and its total blood supply are independent of the external physical work performed by the muscle. These values are determined by the number of excited motor units and the frequency of the cycles of their excitation. It follows /279 that substances that dilate the arterioles of the muscle are not formed during the contractile process itself but already in the preceding stages, probably on excitation of the muscle cell membrane.

3. The dilatation of the blood vessels of a muscle increases with increasing frequency of stimulation of the motor fibers and reaches a maximum at 8 impulses/sec, i.e., still at a subtetanic level of muscle contraction. A further increase in frequency will prolong the recovery period. The former fact indicates that the blood supply of the working muscle follows the principle of "payment in advance", while the latter might be interpreted as the manifestation of a "debt to the blood". This contradiction is explained by subsequent observations.

4. The total resistance of the blood vessels of a muscle decreases in direct proportion to the number of contracting motor units. At the same time, with increasing number of units that have performed work, the duration of the recovery period increases linearly. To explain the former fact, it is sufficient to assume that to each motor unit there corresponds a functionally discrete "vascular unit", i.e., the arterioles that become dilated are those in direct contact with the excited muscle cells. The second fact leads to the converse assumption that the influence responsible for the dilatation of the blood vessels around active motor units is somehow transmitted to all blood vessels of the muscle, so that they will "remember" the number of contracting units of the entire mass.

5. In the decline in vasodilatation during the period of recovery, two components can be distinguished, a fast and a slow one. The former proceeds at /280 constant rate, independent of the number of units that have performed work; the second is detected when 25% of the units or more are turned on and persists longer, the greater the number of units that have functioned. The fast component is believed to correspond to the restoration of the lumen of the arterioles in direct contact with the muscle cells (proximal network of vessels), and the slow component to the gradual constriction of the arterial vessels carrying the blood to the former (distal network of blood vessels). The hypothesis that the vasodilatation is propagated from the proximal network to the distal network eliminates the contradiction mentioned in Paragraph 4, and furnishes an explanation for the fact that the increase in frequency of the impulses in the motor fibers prolongs the period of recovery (Paragraph 3), without having recourse to the hypothesis of "blood debt".

6. With continuous isotonic contraction of a muscle, the blood flow, which increases in the beginning, is maintained at that level as long as the contraction persists. On its elongation, the duration of the period of recovery increases, reaching a maximum at a 1 - 3 min contraction. A further lengthening of the contraction (to 30 min) will not increase the duration of the recovery period nor the total blood supply during that period. These facts cannot be explained on the basis of the concept of the "blood debt" but must use the hypothesis of the propagation of vasodilatation to a distal net of blood vessels as basis.

7. The rapid constriction of the blood vessels of muscles on termination of the exertion would subject the cardiovascular system to dangerous overloads. The slow decline of working hyperemia, evidently due to the peculiar properties of the distal network of blood vessels, constitutes one of the adaptations /281 ensuring gradual transition of the circulation from the state characteristic of muscular activity to the state of rest. The intensification of the blood flow in the muscles after work is not necessary for "payment of the blood debt", since it can also be paid by more complete extraction of oxygen. In the light of the above facts, the concept of "blood debt" appears unjustified.

ACTIVITY OF THIAMINASE UNDER CONDITIONS OF FLUCTUATING OXYGEN SUPPLY TO THE ORGANISM

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In considering the problem of regulation of the oxygen regime of the organism, one necessarily comes to the laws of regulation of oxidative processes in the tissues. In connection with establishing collateral routes of carbohydrate metabolism, the question of their correlation becomes acute. It had to be postulated that changes in the function of the various routes of carbohydrate oxidation, depending on the conditions of oxygen supply to the tissues and the direction of the metabolic processes in ontogenesis, may also have an effect on the activity of the corresponding enzymes.

Ferments containing thiamine pyrophosphate, pyruvate dehydrase, α-ketoglutarate dehydrase, and transketolase as coenzymes catalyze a number of key steps in tissue oxidation processes. It is well known that pyruvate dehydrase accomplishes the oxidative decarboxylation of pyruvate and converts it into acetyl-CoA, combining glycolysis with the ring of the tricarboxylic acids, one of whose enzymes is α-ketoglutarate dehydrase. Transketolase accelerates the extremely important reactions of the pentose phosphate route of glucose oxidation.

The object of the present work was to study the activity of thiaminase under the conditions of diminished oxygen supply to the organism, in animals of various age groups. Since the thiamine enzymes participate in various oxidative routes of carbohydrate metabolism, they may be regarded as indices of their /283 function.

The maximum transketolase activity (TA) of cardiac and hepatic tissues is encountered in newborn (1 - 2 day) puppies and rats. With age, the TA decreases, especially in the myocardium and less markedly in the liver. The TA declined during individual development in the dog brain, but did not substantially vary in the rat brain. The activity of pyruvate dehydrase and α-ketoglutarate dehydrase in the liver and myocardium of newborn animals is less than in old animals.

These data justify the postulation that the activity of the pentose phosphate route of carbohydrate oxidation is increased in the tissues of newborn animals, while the tricarboxylic acid cycle is less active.

Acute hypoxia has a different effect on the activity of these enzymes in the dog during ontogenesis. In the newborn puppy, there were no substantial changes in the TA in the tissues of heart, brain, and liver during acute hypoxia.

In 2 week old puppies, the TA increases in the heart tissues and decreases somewhat in the cerebral cortex and brain stem. In adult dogs, there is a marked increase of TA in the tissues of the heart, a slight increase in the brain, and a tendency to decline in the liver. These data indicate that the ability of the heart and brain tissues to activate the pentose phosphate cycle in acute hypoxia increases with age.

At the same time, in acute hypoxia we observed a decline in pyruvate dehydrase and α-ketoglutarate dehydrase in the myocardium and liver. These changes are more pronounced in young animals.

To study the adaptation to hypoxia in the activity of thiaminase of the rat tissue, the rats were kept in the altitude chamber at the simulated altitude /284 of 8000 meters for six hours each day and were examined 7, 14, and 28 days after the beginning of the experiment. After seven days, we observed a rise of TA in the heart, brain, and liver, and also on activation of pyruvate dehydrase and α-ketoglutarate dehydrase in the myocardium. In later periods, the TA increased in the brain and liver, and the activity of the thiaminase of the heart decreased somewhat.

To define the role of the thiamine enzymes in the mechanism of resistance of the animals to hypoxia, we studied the survival of rats in acute B_1-avitaminosis, induced by injecting the B_1 antivitamin, oxythiamine. The preparation was injected intraperitonially in doses of 200 mg/kg for two days. The injection of the oxythiamine into adult rats, adapted to hypoxia, lowered the survival rate in acute hypoxia. We noted a marked decrease of TA in the heart, and some decrease of TA in the liver. The TA in the brain was substantially unchanged. This confirms the significance of the activation of the thiamine enzymes in increasing the resistance of adult rats to hypoxia.

Other results were obtained in a study of the action of oxythiamine on the organism of newborn rats. Oxythiamine considerably lowered the TA in the heart, liver, and brain, reduced the growth of the animals, and increased their survival under conditions of acute hypoxia. This feature of the action of oxythiamine on newborn animals is apparently a consequence of the sharp decrease in the energy requirements of the tissues, in connection with the decrease in the biosynthesis processes and the decline in the metabolic activity of the brain.

These data show that the resistance of animals to hypoxia largely depends on the functions of these enzymatic systems. The intense pentose phosphate cycle in the newborn animals, and its activation during hypoxia in the adult animals, may possibly increase the resistance of the organism to oxygen insufficiency. /285 We cannot disregard the significance of the pentose phosphate cycle in the output of energy; in fact, it may possibly also encourage the elimination of lactic acid.

OXYGEN DEMAND AND CIRCULATION /286

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The oxygen demand of the organs and tissues, determined by their functional features and by the needs of the organism as a whole, is satisfied by the coordinated course of numerous processes. The significance of the circulation is very great here and, in many physiological and pathological conditions, adjusts the supply of oxygen to the demand.

The rate of delivery of the required amount of oxygen to the tissues depends on the condition of the capillary network and on the partial oxygen pressure (pO_2) in the blood of the capillaries. The limiting factor here is the pO_2 in the venous blood of the capillaries, i.e., a quantity approximating the pO_2 of the venous blood, differing from organ to organ and relatively constant for the mixed venous blood. Constancy of the pO_2 of the mixed venous blood is maintained by regulation of the circulation in accordance with the oxygen demand, and depends primarily on the volume rate of blood flow, of which the index is the cardiac minute volume (MV). Thus, of the numerous parameters of the circulation, the MV and its distribution among the organs as well as the state of the capillary network are of decisive importance for satisfying the oxygen demand.

The fact that the blood circulation is regulated in accordance with the oxygen demand is well established and is primarily evidenced by the direct /287 relation between oxygen consumption and MV. However, the problem of the MV cannot be considered solved. For a long time, its study was neglected in favor of numerous investigations on the regulation of the arterial pressure (AP). Without making a choice between the merits of these factors, it should be noted that the organism, in regulating the adequate oxygen demand, requires the MV rather than the level of the AP as such. Under various conditions, when the normal correlation between MV and AP is disturbed, a favorable outcome is possible in cases where the proper MV is maintained, even at an abnormal level of the AP; in the opposite cases (when a normal AP is maintained at a greatly disturbed MV), prolonged maintenance of normal oxygen utilization and of life is impossible. Of course, the necessary MV is ensured only if the AP is kept within certain limits; these limits have their own significance.

The most widely accepted ideas of the most schematic pattern of regulation of the MV can be formulated as follows: The principal object of central regulation is the AP level; this parameter is kept relatively constant by varying the total peripheral resistance, the flow of blood to the heart from the low-pressure system, and the contractile function of the myocardium. It is assumed here that the MV is regulated only to the extent required for maintenance of the normal AP level. According to this concept, the correspondence of the MV to the oxygen demand is established by regulation of the local (original) vascular resistance. The oxygen demand of each organ directly (over the action of the pO_2) or indi-

rectly (for example, over the metabolites) varies the local vascular resistance and the state of the capillary network, which, at an adequate level of the AP, ensures a blood flow meeting the oxygen requirement. /288

According to these ideas, the CNS requires no information on the oxygen regime and its related parameters in order to regulate the MV. The universal applicability of this scheme raises serious doubts, like the MV-independent regulation of the AP level.

In contrast to this scheme, we might assume the arrival of direct or indirect information on the oxygen utilization in the central apparatus of circulatory regulation (for instance, data on the pO_2 in the tissues or in the venous blood).

Such an assumption, for which there are many substantiations, will require a clarification of the nature and mechanism of transmission of such information. The chemoreceptors of the arterial system, for which the pO_2 of the arterial blood is an adequate stimulus, in contrast to the regulation of respiration, cannot ensure a regulation of the MV adequate for the oxygen demand.

Data on the existence of such receptors in the tissues, or in sections of the cardiovascular system supplied with mixed venous blood, are incomplete; research in this direction is continuing and appears quite promising.

VARIATION OF THE LABILITY OF THE NEUROMUSCULAR APPARATUS OF ATHLETES AFTER PERFORMANCE OF A STANDARD TASK UNDER CONDITIONS OF OXYGEN INSUFFICIENCY

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Many forms of muscular work, from high power to maximum power, are performed by athletes under conditions of more or less pronounced oxygen insufficiency. In this connection, studies on the fluctuations of the lability of the neuromuscular apparatus (NMA) in performing the standard task of athletes under conditions of hypoxia are of great interest.

In the available literature, we found no papers devoted to the study of the variation of functional insufficiency. The following topics were scheduled: 1) study of the influence of the standard task, performed under the conditions of induced hypoxia, on the variation of the lability parameters: optimum and maximum rates; 2) study of the influence of work, performed under oxygen insufficiency, on the variation of the values and duration of the peak potential of the bioelectric response: rheobasis and chronaxia.

We examined 60 athletes (71 observations in all) ranging in age from 18 to 28. All subjects were basically healthy and most of them were rather highly trained.

The athletes performed repeated work on the bicycle ergometer at a rate of 1000 kgm/min for a period of 3 min. The first task was performed under the ordinary regime of breathing atmospheric air, and three others while inhaling a gas mixture containing 15% oxygen and 85% nitrogen. The gas mixture was prepared in an apparatus for gas narcosis, specifically modified by us for that purpose. The composition of the mixture before each task was checked in the Haldane /290
chamber and the "Spirolite" spirograph. The analysis of the expired air was continuously recorded during rest, during the task, and during recovery on the "Spirolite". During these periods, the oxygen saturation of the blood was recorded by an oxyhemograph 036-M.

To evaluate the action of the standard task, performed under conditions of oxygen insufficiency, we investigated the lability of the NMA by the electric stimulus method. The most excitable point was found on the right head of the quadriceps muscle of the left femur by means of a special movable probe, after which the rheobasis and chronaxia were determined. The value of the stimulus equaled three rheobases, and the duration one chronaxia. The frequency of the electrical square pulses ranged from 6 to 200/sec. The time interval between the series was 10 - 12 sec. Electric stimulation was applied 5 min before the beginning of the task and 10 min after its completion. In 14 cases, we performed a control electric stimulation after the first task which had been per-

formed while breathing atmospheric air.

An analysis of our data showed the following: The standard muscular task performed by the athletes under conditions of hypoxia was accompanied by a decline in the level of oxygen saturation of the arterial blood to 87 - 50%. The initial level of lability, determined from the optimum and maximum rhythms of the bioelectric response (both per second and in absolute value over the minimum time segment), and also from the value and duration of the peak potential in the athletes, was not the same. In 17 subjects (mainly swimmers and light athletes), the initial level of lability was high: The optimum rhythm ranged from 80 - 140 pulses per second, with a maximum of 160 - 200 pulses. In most of the athletes (55% of the subjects), we found a moderate level of lability: optimum rhythm /291 40 - 80 pulses, maximum 120 - 160. The subjects with a low optimum rhythm and a high maximum, and conversely, were assigned to this group. The third group of athletes (10 subjects) were mostly boxers who showed a low index of NMA lability. Their optimum rhythm was below 40/sec, and the maximum below 120. It should be noted that, while the subjects of the first two groups were highly trained, the subjects of the third group were in a moderate state of training.

After a task performed under conditions of oxygen insufficiency, the lability most often declined in the boxers and less often in the light athletes. In the subjects of Group 1, we noted an increase in the peak potential of the bioelectric response, while in the subjects of Group 2 it was unchanged and in Group 3, declined. It must be noted that the task performed while breathing atmospheric air was accompanied either by an increase in the parameters of the optimum and maximum rhythms and in the values of the peak potential, or by their constancy.

The character of the direction of the changes in the duration of the peak potential after performance of the task under hypoxia was as follows: In Group 1, we noted a decrease in the duration of the peak potential to 50% of its initial value. In contrast, Group 3 showed an increase of up to 200% in the peak potential. Here again, Group 2 occupied an intermediate position. The control group showed constant or diminished duration of the bioelectric response.

The variations in the rheobasis and the chronaxia, after a task performed under conditions of oxygen, are striking. In the subjects of Group 1, the /292 rheobasis increased somewhat while the chronaxia remained unchanged. In Group 2 and Group 3, the rheobasis and chronaxia varied in the same direction: The rheobasis fluctuated slightly upward and downward, while the chronaxia did not change or else increased slightly. These indices were unchanged in the control group after work, while breathing atmospheric air.

Thus the task performed under hypoxic conditions leads to sharper shifts of the NMA lability, as a function of the individual characteristics of the subjects, their degree of training, and their special field of athletics.

CONTRIBUTION TO THE QUESTION OF TRANSIENT PROCESSES IN THE FIRST STAGE OF THE OXYGEN REGIME CONTROL SYSTEM OF THE ORGANISM

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Studies of the oxygen regime control system of the organism, conducted at the Institute of Physiology, UkrSSR Academy of Sciences, by N.V.Lauer, A.Z. Kolchinskaya, and the present author, require the consideration and mathematical description of the transient processes in each link of this system.

The first link of the control system of the oxygen regime of the organism is the lung reservoir. The input of this unit is fed with external air whose oxygen is determined by two main parameters: partial pressure $p_I O_2$ and volume of air entering the lung per minute.

The output of the unit discharges alveolar air, with the parameters $p_A O_2$ and $\dot{V}_A O_2$.

The mathematical dependence of output on the input of this link, for stationary regimes, was first calculated by I.M.Sechenov in 1880, who called it the "law of stationary composition of the alveolar air". He derived an expression for the volume of oxygen in the alveolar air, after a steady state is reached quietly*. Without making use of all the considerations by Sechenov, we will derive this expression in a somewhat different manner. During one respiratory cycle, a volume of air V_{AI} with a percentage oxygen content of $F_I O_2$, enters the alveolar space from the external air, a volume of air V_{AE} with an oxygen /294 content $F_A O_2$ is eliminated, and a volume of oxygen $\frac{\dot{V}_t O_2}{f}$ is utilized by the organism, where $\dot{V}_t O_2$ is the oxygen consumption per minute and f is the respiratory rate.

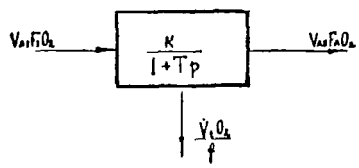

Fig.1

The equation of equilibrium has the form

* I.M.Sechenov: "Oxygen Tension in the Pulmonary Air under Various Conditions" (O napryazhenii kisloroda v legochnom vozdukhe pri raznykh usloviyakh). "Vrach", No.43, 1880.

$$V_{AI} F_I O_2 - V_{AE} F_A O_2 - \frac{\dot{V}_t O_2}{f} = 0 \qquad (1)$$

At the end of the expiration, the volume of oxygen in the alveolar air will be $V_R F_A O_2$, where V_R is the volume of alveolar air after quiet exhalation. Multiplying and dividing the second term of the equation by V_R and solving it for $V_R F_A O_2$, we obtain the expression for the volume of oxygen in the alveolar air at the end of one expiration, in the form obtained by I.M.Sechenov:

$$V_R F_A O_2 = \left(V_{AI} F_I O_2 - \frac{\dot{V}_t O_2}{f}\right) \frac{V_R}{V_{AE}} \qquad (2)$$

Equation (2) is the equation of statics of the link under consideration. The static characteristic of the dependence of the oxygen content of the alveolar air on the oxygen content of the atmospheric air can be described by the equation of a straight line:

$$F_A O_2 = \frac{V_{AI}}{V_{AE}} F_I O_2 - \frac{\dot{V}_t O_2}{V_{AE} f} \quad ,$$

where $\frac{V_{AI}}{V_{AE}} = K$ is the static amplification factor of the link (Fig.2). /295

Sechenov termed the quantity $V_R F_A O_2$ the stationary volume of oxygen in the alveolar air and showed that, after a change in the conditions of respiration, it would reach a new steady state within 3 - 4 min, whose value would approach, at the limit, the sum of the terms of a convergent geometrical progression. The ratio of the progression, $q = \frac{V_R}{V_{AE} + V_R} < 1$, and its product equals the right-hand side of eq.(2). It was not Sechenov's object to study the character of the transient process.

Pursuing his reasoning further, let us try to find the time variation of the O_2 content of the alveolar air, on transition from the old steady state $V_R F_A O_2'$ to the new steady state $V_R F_A O_2''$, due to a decrease in the oxygen content of the inspired air from the value $F_I O_2'$ to the value $F_I O_2''$ where $F_I O_2'' < F_I O_2'$.

The equation derived by Sechenov to describe this transition consists of two terms: the product of the terms of the geometrical progression plus the old steady state $V_R F_A O_2'$, multiplied by the ratio of the progression q to the n^{th} power, where n is the number of respiratory cycles:

$$V_R F_A O_2 = \frac{a_1}{1-q}\left(1 - q^n\right) + V_R F_A O_2' \cdot q^n \quad .$$

where the first term of the progression $a_1 = \left(V_{AI} F_I O_2'' - \frac{\dot{V}_t O_2}{f}\right) \frac{V_R}{V_{AE} + V_R}$ and the ratio of the progression $q = \frac{V_R}{V_{AE} + V_R}$. However, $\frac{a_1}{1-q}$ is the limit to which the product of the progression approaches as n increases, and equals the new value $V_R F_A O_2''$.

Thus,

$$V_R F_A O_2 = V_R F_A O_2'' (1 - q^n) + V_R F_A O_2' q^n$$

or

$$V_R F_A O_2 = (V_R F_A O_2' - V_R F_A O_2'') \left(\frac{V_R}{V_{AE} + V_R}\right)^n + V_R F_A O_2'' ,$$

while

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$$F_A O_2 = (F_A O_2' - F_A O_2'') \left(\frac{V_R}{V_{AE} + V_R}\right)^n + F_A O_2'' . \qquad (3)$$

It will be clear from eq.(3) that the decrease in the oxygen content of the alveolar air, when the oxygen in the inspired air decreases, is described by an exponential function. At the beginning of the transient process, at n = 0, the content of oxygen $F_A O_2$ ($V_R F_A O_2$) equals its initial value $F_A O_2'$ ($V_R F_A O_2'$); at the end of the process (theoretically at n = ∞, but practically at n = 25 - 30), it will become equal to $F_A O_2''$ ($V_R F_A O_2''$). The rate of the process is determined by the ratio $\frac{V_R}{V_{AE} + V_R}$. The smaller the ratio of the volume of the alveolar air V_R to the volume of the expired air V_{AE}, the more rapid will be the transient process of establishing a new stationary state of the oxygen parameters in the alveolar air.

The equation of the transient process may be more simply derived by using the ordinary method of differential equations. Let us write, on the basis of eq.(1),

$$\left(V_{AI} F_I O_2 - V_{AE} F_A O_2 - \frac{\dot{V}_t O_2}{f}\right) dn = d(V_R F_A O_2) \qquad (4)$$

i.e., the increment of the stationary volume of oxygen in the alveolar air $d(V_R F_A O_2)$ during the part dn of the respiratory cycle equals the difference between the oxygen delivered and the sum of the oxygen eliminated with the expired air and the oxygen consumed, during the same part of the cycle. After transformations, eq.(4) takes the following form:

$$\frac{V_R}{V_{AE}} \frac{d(V_R F_A O_2)}{dn} + V_R F_A O_2 = \left(V_{AI} F_I O_2 - \frac{\dot{V}_t O_2}{f}\right) \frac{V_R}{V_{AE}} \qquad (5)$$

where the quantity $\frac{V_R}{V_{AE}}$ will be the time constant T of the link. Solving this equation for $V_R F_A O_2$ and determining the integration constant from the initial conditions, we have the following expressions:

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$$V_R F_A O_2 = (V_R F_A O_2' - V_R F_A O_2'') e^{-\frac{n}{T}} + V_R F_A O_2'' \qquad (6)$$

and

$$F_A O_2 = (F_A O_2' - F_A O_2'') e^{-\frac{n}{T}} + F_A O_2''$$

It is clear from these expressions that, during the time of the transient process, the change in oxygen content of the alveolar air proceeds by an exponential law with the time constant $T = \frac{V_R}{V_{AE}}$ determining the rate of establish-

ment of the new steady state. The number of respiratory cycles, at the end of which the system will pass to a new steady state, is $n_y = 3T$. To express the time constant T in minutes, it must be divided by the number of respiratory cycles per minute f:

$$T_{(M)} = \frac{\dot{T}}{f} = \frac{V_R}{V_{AE} \cdot f} = \frac{V_R}{\dot{V}_A},$$

since $V_{AE} f = \dot{V}_A$ is the alveolar ventilation. Thus, the time constant $T_{(M)}$ and the time of establishment of the process $t_y = 3T_{(M)}$ are directly proportional to the volume of the alveolar air and inversely proportional to the alveolar ventilation.

Equations (3) and (5) show great similarity in the mathematical description of the transient process in the first link of the oxygen-transport system, despite the different approaches to their derivation. Substituting the numerical values, we obtain practically the same time of establishment of the steady state, no matter which of the two expressions is used for the calculation.

Figure 3 shows curves of the transient processes calculated from eqs.(3) and (5). Nowhere is the difference between the values of the function F_AO_2 greater than 5%.

The transfer function of this link, on the basis of eq.(5), will be /298

$$\frac{Y(p)}{X(p)} = \frac{K}{1+Tp} \qquad (7)$$

where p is the Laplace differential operator; K is the amplification factor of the unit, and Y(p) and X(p) are the Laplace transformations for the output and input functions.

It is clear from eqs.(5) and (7) that, in this consideration, the first link of the oxygen-transport system is an inertial (aperiodic) member of first order, with the time constant $T = \frac{V_R}{V_{AE}}$ and the amplification factor $K = \frac{V_{AI}}{V_{AE}} > 1$. All preceding derivations were based on the assumption that the quantities V_R, V_{AI}, and V_{AE} remained constant throughout the course of the transient process. Actually, this is not so. The oxygen regime regulatory system, on variation in the conditions of respiration, tends to maintain the composition of the alveolar air constant by acting on the respiratory center and by varying the alveolar ventilation as well as the frequency and depth of respiration.

Since all preceding derivations have been based on a single respiratory cycle, the variation in respiratory rate will have no effect on their accuracy. However, the variation in the volumes V_R, V_{AI}, and V_{AE} under the action of the control influences will transform the linear differential equation (5) into an equation that is substantially nonlinear.

The time constant T' and the amplification factor K' of the unit will be variable, depending on the changes in the oxygen content of the alveolar air:

$$T' = \frac{\partial V_{AE}}{\partial F_A O_2} : \frac{\partial V_R}{\partial F_A O_2}, \qquad K' = \frac{\partial V_{AI}}{\partial F_A O_2} : \frac{\partial V_{AE}}{\partial F_A O_2}.$$

METHOD OF EVALUATING THE FUNCTION OF EXTERNAL RESPIRATION OF MAN IN FLIGHT

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The methods and technical means used today for investigating the function of the external respiration of man in flight only permit recording of the respiratory rate and the relative depth of respiration.

More precise studies based on the use of known methods of measurement and recording of the external respiration indices are not applicable to the conditions of flight, owing to the bulk, weight, and power consumption of the physiological apparatus needed.

The method of evaluating the function of external respiration of man according to the velocity-volume diagram, which we have studied with reference to flight conditions, yields the following group of pneumotachometric indices: vital capacity, current respiratory volumes, complementary and supplementary air, maximum and reserve rates of inspiration and expiration, respiratory frequency, pulmonary ventilation, etc.

We have developed and built a working model of an instrument for investigating the function of the external respiration by this method, whose weight and size permit its inclusion in airborne equipment.

Under experimental laboratory conditions, the velocity-volume diagrams are recorded by photographing the screen of an electronic oscillograph. The apparatus also permits recording the curves for variation in volume and velocity /300 of the inspired and expired air, from the readings of ink-writing or loop recorders.

In flight or stand tests, the preliminary recording of the initial data on a miniature magnetic recorder is followed by its work-up under laboratory conditions.

This method has been approved under laboratory and special conditions. Data of the external respiration of man in the state of rest, under physical stress, and during inhalation of hypoxic mixtures have been obtained and processed.

The widespread introduction of this method of investigating the function of external respiration is somewhat limited by the necessity of manual work-up of the pneumotachograms, involving rather tedious and monotonous mental work, performed according to definite rules. The results of interpretation of the readings can be analyzed only after completing the recording, which does not always meet the experimental requirements.

To obtain the numerical values of the pneumotachometric indices during

actual collection of the experimental data, we developed a method of automatic processing of these functions of the external respiration of man, allowing the investigator to make an operative evaluation of the condition of the respiratory mechanism and to follow its variations.

REDOX REACTIONS WITH PARTICIPATION OF EXOGENOUS CYTOCHROME C AND QUESTIONS OF OXYGEN EXCHANGE

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The mechanism of electron transfer from the substrate of respiration to molecular oxygen is rather well known today. Cytochrome oxidase, which performs a terminal function, plays the most important part in effecting the mechanism of respiration of animal tissues.

In contrast to animal tissues, the mechanism of biological oxidation in plants is more complex. The capability of plants to accomplish photosynthesis and to fix, in the chloroplasts, the energy of the macroergic bonds of ATP, by means of the reaction of photosynthetic phosphorylation differs markedly from oxidative phosphorylation, which likewise proceeds in plants, and makes a profound impression on all aspects of the processes of the oxygen exchange mechanism. The major difference between plants and animals in this respect is the large number of routes of oxidation of substrates and the existence of terminal oxidases that do not occur in animal tissues; however, as in the case of animals, cytochrome oxidase has been the only substance for which it can be shown at present that it can accomplish phosphorylation involving electron transfer in plants.

We studied the redox transformations of cytochrome C in various reactions, relating both to the mechanism of respiration and to photosynthesis. We used cytochrome C of animal origin, closely resembling the native cytochrome of plants. We showed that, on illumination of chloroplasts, reduction of cytochrome C takes place, with inverse oxidation after the light is cut off, and /302 that the cycle can be repeated many times. The photoreduction of cytochrome probably proceeds according to the type of Hill reaction. Dark oxidation of cytochrome C introduced from outside is accomplished in the chloroplasts by a cytochrome oxidase with properties different from those of the cytochrome oxidase of animal tissues and the cytochrome oxidase of plant mitochondria. In the chloroplast of the pea, we found a peculiar cytochrome oxidase, which manifests its activity after inhibition of the ordinary cytochrome oxidase by cyanide, and only when illuminated.

A comparative study of the set of cytochromes in various organoids of plants and animals, and a comparison of their functions, will help to increase our knowledge of the mechanism of biological oxidation.

SOME ELECTRODE PAIRS FOR OXYGEN MEASUREMENT IN LIVING TISSUES /303
(Abstract of Paper)

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The rapid adoption of the polarographic method of measuring oxygen in tissues in experimental and clinical practice has aroused interest in oxygen sensors (electrodes), and in particular in the materials for their manufacture.

Platinum, gold and copper amalgam are used as materials for polarized electrodes. Unpolarized electrodes in circuits with an external emf may be of calomel or silver chloride; the materials for unpolarized electrodes in batteryless circuits may be iron or cadmium.

We made a comparative study of these electrode pairs, in which the polarized electrodes were in the form of open microelectrodes. We studied the behavior of the potentials of the reference electrodes in various media and compared the diffusion current densities in physiological salt solution and blood serum.

Based on our study we conclude that these electrode pairs are, in principle, electrochemically identical. However, in the practical use of such electrode pairs, certain peculiar features of each of these pairs must be taken into account. For example, in selecting the electrode material, one must take account of the time of intended use of the electrodes in the experiment, the presence /304 of high pO_2 (for example, in the altitude chamber), the tendency to "poisoning" of polarized electrodes, etc. It has been found that a copper amalgam electrode is unsuitable for prolonged insertion in tissue; in the presence of large amounts of organic surfactants in the tissue, platinum is poisoned more strongly than other electrodes; the self-potential of the iron electrode is sensitive to oxygen pressure; the electrode potential of silver chloride electrodes is unstable if carelessly handled; the calomel electrode is awkward and complicated to use in measurements on animals, etc.

The choice of an electrode pair for tissue oxygen measurement must therefore be made dependent on the experimental conditions.

OXYGEN SATURATION OF THE BLOOD AS A FACTOR IN REGULATION OF THE PROCESS OF BIOSYNTHESIS AND UTILIZATION OF THE PROTEIN COMPONENTS OF THE BLOOD

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Biosynthesis of the protein components of blood coagulation proceeds primarily in the liver parenchyma and in the reticuloendothelial system. In the liver parenchyma, the following are synthesized: accelerator-globulin (factor V) which belongs to the globulin group; proconvertin (factor VII), which is found in the β-globulin fraction; prothrombin-α_2-globulin and fibrinogen, which are also globulins but which occupy their own specific zone on the electrophoregram. In the reticuloendothelial system, the biosynthesis of antihemophilic globulin (factor VIII) takes place, which belongs to the globulins and moves with the α- and β-globulins in electrophoresis.

Muscular activity, as is well known, is accompanied by hypoxemia. When the oxygen level of the blood drops by 9 - 10%, the protein concentration undergoes a number of changes. The concentration of the protein components of the blood, synthesized in the liver parenchyma, is substantially decreased and drops by 15 - 25% within 3 hrs after the exercise, except for the fibrinogen whose level does decline after work but returns to its initial value within 90 min. It is possible that, under the conditions of muscular activity, there is not only /306 a suppression of biosynthesis in the liver parenchyma but also an intensified protein utilization. However, simulated ascent of subjects of various ages in the altitude chamber to 4000 m induced a decrease in the concentration of prothrombin, fibrinogen, and proconvertin, indicating the dominant role of blood oxygenation in these changes. An entirely different picture is observed in the activity of the cells of the reticuloendothelial system. The concentration of antihemophilic globulin increases with a decline in the oxygen blood level, the increase being directly proportional to the extent of that decline.

The exceptional sensitivity of these cells to a depletion in blood oxygen has been demonstrated in experiments in which, during oxygen inhalation, the oxygenation of the blood decreased by not more than 2%. Under these conditions, the cells of the liver parenchyma did not react by decreasing the processes of biosynthesis, whereas the synthesis of the antihemophilic globulin in the Kupffer cells increased.

Experiments on rabbits at 7500 m in the altitude chamber or in the hypoxic chamber at 7% oxygen content showed an analogous picture.

Of interest here are cases of afibrinogenemia, i.e., the complete disappearance of blood fibrinogen following a stay in the hypoxic chamber. It is possible that oxygen insufficiency in the blood of the parturients may play an important role in the occurrence of hemophilia in families as a result of afibrinogenemia.

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